Universidade do Minho
Escola de Medicina

Sónia Maria Gomes de Amaral Ferreira

Cognitive and emotional regulation in stress and obsessive-compulsive disorder

outubro de 2020

Cognitive and emotional regulation in stress and obsessive-compulsive disorder
Sónia Maria Gomes de Amaral Ferreira
UMinho | 2020

Universidade do Minho
Escola de Medicina

Sónia Maria Gomes de Amaral Ferreira

Cognitive and emotional regulation in stress and obsessive-compulsive disorder

Tese de Doutoramento
Doutoramento em Ciências da Saúde

Trabalho efetuado sob a orientação do
Professor Doutor Pedro Ricardo Luís Morgado
e do
Professor Doutor José Miguel Gomes Moreira Pêgo

outubro de 2020

DIREITOS DE AUTOR E CONDIÇÕES DE UTILIZAÇÃO DO TRABALHO POR TERCEIROS

Este é um trabalho académico que pode ser utilizado por terceiros desde que respeitadas as regras e boas práticas internacionalmente aceites, no que concerne aos direitos de autor e direitos conexos.
Assim, o presente trabalho pode ser utilizado nos termos previstos na licença abaixo indicada. Caso o utilizador necessite de permissão para poder fazer um uso do trabalho em condições não previstas no licenciamento indicado, deverá contactar o autor, através do RepositóriUM da Universidade do Minho.

Licença concedida aos utilizadores deste trabalho

Atribuição-NãoComercial-SemDerivações

CC BY-NC-ND

https://creativecommons.org/licenses/by-nc-nd/4.0/

ACKNOWLEDGMENTS

To my parents to whom I owe everything I am (*Para os meus pais, a quem devo tudo o que sou*). To my best friends forever, my sisters Fatita and Susana and brothers Zé Luís, Pedro, and Tiago. To Chiquitita and Mateus for reminding me daily of the little joys of life. To my Riri, my new family, for enduring all the obsessive and stressful moments (and to his supercomputers and delicious dinners). To the fabulous neuroimaging team, you rock (scientifically and non-scientifically speaking)! Maria, Mafalda, and Rita thank you for your precious neurofeedback magic. To my dear *Poker de Damas*, for all the laughs and foolishness. To all the participants and their families for their voluntary contribution to our studies. To the ICVS, *Hospital de Braga*, and 2CA friends, particularly Celina for all the help and companionship during the magnetic resonance sessions. To Professors João Relvas and Nuno Sousa for all their thoughtful insights into this work. To José Miguel Pêgo for all the support and mentorship during my Ph.D. journey. To Pedro Morgado for allowing me to walk my path while always supporting and trusting me in the way with great scientific enthusiasm.

The work presented in this thesis was performed in the Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal, the Clinical Academic Center (2CA), Braga, Portugal, and *Hospital de Braga*, Braga, Portugal.

Financial support was provided by grants from the BIAL Foundation, Porto, Portugal (grant PT/FB/BL-2016-206), the 2CA, Braga, Portugal (grant "Treating refractory obsessive-compulsive disorder using real-time functional magnetic resonance imaging neurofeedback"), the Foundation for Science and Technology (FCT), Lisbon, Portugal and the company iCognitus4ALL – IT Solutions, Lda, Braga, Portugal (PD/BDE/127839/2016; School of Medicine's PhDiHES program), by National funds, through the FCT - project UIDB/50026/2020 and UIDP/50026/2020, and by the projects NORTE-01-0145-FEDER-000013 and NORTE-01-0145-FEDER-000023, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF).

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

COGNITIVE AND EMOTIONAL REGULATION IN STRESS AND OBSESSIVE-COMPULSIVE DISORDER

ABSTRACT

The current literature has gathered some evidence of impairments in cognitive regulation processes in obsessive-compulsive disorder (OCD). The inadequate self-regulation of obsessive thoughts leads to states of extreme distress and anxiety. To obtain relief from these negative states, obsessive-compulsive individuals perform rewarding repetitive behaviors. The augmented stress levels associated with OCD may also impact cognitive regulation. However, the neurobiological and behavioral deficits of cognitive regulation in this disorder require further clarification. This thesis provides novel insights into the mechanisms of cognitive regulation of emotion and reward in individuals suffering from OCD and stress. We conducted several experiments using psychometric variables, behavioral outcomes, and functional magnetic resonance imaging. Our findings demonstrated alterations in the activity and functional connectivity of prefronto-parietal brain regions during cognitive regulation tasks in OCD patients. Additionally, we observed deficits in the use of emotion regulation strategies and inflexibility during reward valuation. Moreover, we found that augmented stress levels modulate the interaction between emotion regulation deficits and OCD symptoms and impact reward valuation. Finally, we observed that neurofeedback, an emotion regulation-based treatment where participants self-regulate their brain activity in real-time, improves OCD and stress scores and reverses some of the frontoparietal alterations. The OCD deficits in cognitive regulation may arise from the importance attributed to control intrusive thoughts. These patients are excessively focused on internal states consequently lacking the cognitive flexibility to switch their attentional resources away from thoughts and negative emotional states. Moreover, increased stress levels may lead to an exacerbation of cognitive regulation impairments. Our conclusions support the inclusion of stress management in psychotherapy approaches to improve cognitive regulation skills.

Keywords: cognition; emotion; neurofeedback; OCD; reward

A REGULAÇÃO COGNITIVA E EMOCIONAL NO STRESSE E NA PERTURBAÇÃO OBSESSIVO-COMPULSIVA

RESUMO

A literatura atual evidencia alterações nos processos de regulação cognitiva na perturbação obsessivo-compulsiva (POC). A autorregulação inadequada dos pensamentos obsessivos leva a estados de extrema angústia e ansiedade. Para obter alívio destes estados negativos, os doentes realizam comportamentos repetitivos recompensadores. Os elevados níveis de stresse associados à POC podem também ter um impacto na regulação cognitiva. No entanto, os défices neurobiológicos e comportamentais na regulação cognitiva nesta patologia estão pouco estudados. Esta tese traz uma nova visão sobre os mecanismos de regulação cognitiva da emoção e recompensa em indivíduos com POC e elevados níveis de stresse. Neste trabalho, realizámos várias experiências usando variáveis psicométricas, medidas comportamentais e ressonância magnética funcional. Os resultados mostraram alterações na atividade e conectividade funcional das regiões cerebrais pré-fronto-parietais durante tarefas de regulação cognitiva em indivíduos com POC. Observámos ainda défices no uso de estratégias de regulação emocional e inflexibilidade durante a valorização de recompensas. Verificámos ainda que os níveis de stresse modulam a interação entre os défices na regulação emocional e os sintomas da POC e reduzem a valorização de recompensas. Por último, observámos que o *neurofeedback*, uma nova abordagem de tratamento baseada em regulação emocional na qual os participantes autorregulam a sua atividade cerebral em tempo real, melhora os níveis de POC e stresse e reverte algumas das alterações frontoparietais. O impacto da POC na regulação cognitiva pode advir da importância atribuída ao controlo dos pensamentos intrusivos. Os doentes estão excessivamente focados em estados internos e, consequentemente, carecem de flexibilidade cognitiva para redirecionar os recursos atencionais dos pensamentos e estados emocionais negativos. Além disso, níveis elevados de stresse podem levar à exacerbação dos défices na regulação cognitiva. As nossas conclusões sustentam a inclusão de técnicas de gestão de stresse nas abordagens de psicoterapia para melhorar a capacidade de regulação cognitiva.

Palavras-chave: cognição; emoção; neurofeedback; POC; recompensa

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

A

ACC - anterior cingulate cortex

ACTH - adrenocorticotropic hormone

B

BAI - Beck Anxiety Inventory

BDI - Beck Depression Inventory

BMI - body mass index

C

CBT - cognitive-behavioral therapy

D

dlPFC – dorsolateral prefrontal cortex

dmPFC - dorsomedial prefrontal cortex

DSM - Diagnostic and Statistical Manual of Mental Disorders

E

EEG - electroencephalography

ERP - exposure-response prevention

ERQ - Emotion Regulation Questionnaire

F

FC - functional connectivity

fMRI - functional magnetic resonance imaging

FPN - frontoparietal network

G

GLM - general linear model

gPPI - generalized psychophysiological

H

HARS - Hamilton Anxiety Rating Scale

HDRS - Hamilton Depression Rating Scale

HPA - hypothalamic-pituitary-adrenal

I

ICD - International Classification of Diseases

M

MNI - Montreal Neurologic Institute

MRI – magnetic resonance imaging

O

OC – obsessive-compulsive

OCD – obsessive-compulsive disorder

OCI-R - Obsessive-Compulsive Inventory-Revised

OCD&RD - obsessive-compulsive and related disorders

OFC – orbitofrontal cortex

P

PFC - prefrontal cortex

PI-WSUR - Padua Inventory–Washington State University Revision

PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses

PSS-10 – 10-items Perceived Stress Scale

S

SSRI - selective serotonin reuptake inhibitor

SSRIs - selective serotonin reuptake inhibitors

STAI - State-Trait Anxiety Inventory

V

vlPFC – ventrolateral prefrontal cortex

vmPFC - ventromedial prefrontal cortex

Y

Y-BOCS - Yale-Brown Obsessive Compulsive Scale

LIST OF FIGURES

INTRODUCTION

CHAPTER I

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

DISCUSSION, FUTURE PERSPECTIVES, AND CONCLUSIONS

LIST OF TABLES

CHAPTER I

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

INTRODUCTION

1. Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a severe and incapacitating disorder that affects 1 to 3% of the general population. Patients suffer disturbances in social, family, and career contexts (Robbins et al., 2019; Stein et al., 2019). The unawareness about OCD in society, the patients' stigma, and the lack of accessible treatments are factors contributing to the health-economic burden of this disorder (Stein et al., 2019).

OCD arises from an interplay between genetic and environmental factors and usually develops between childhood to early adulthood. Past research has identified alterations in genes influencing glutamatergic, serotonergic, dopaminergic, and gamma-aminobutyric acid mechanisms, providing evidence of glutamatergic and dopaminergic hyperactivity, impairments in serotonin-related synaptic function, and deficits in the inhibition of synaptic activity. Environmental risk factors for OCD include early life stressful and traumatic events (Adams et al., 2018; Alemany-Navarro et al., 2020; Dougherty et al., 2018; Robbins et al., 2019; Stein et al., 2019).

OCD is defined by persistent, intrusive, and unwanted thoughts or images that generate elevated levels of anxiety and cause distress – obsessions. To reduce this aversive states of anxiety and distress, OCD patients commonly performed ritualistic mental acts or behaviors - compulsions (American Psychiatric Association, 2013; Stein et al., 2019). Diverse combinations of obsessions and compulsions give rise to a heterogeneous manifestation of OCD (obsessions/compulsions dimensions – contamination obsessions/cleaning and washing compulsions; harming obsessions/checking compulsions, symmetry obsessions/repeating, ordering and counting compulsions; sexual, religious, and aggressive obsessions/reassurance-seeking behavior or mental acts; avoidance behavior) (Alemany-Navarro et al., 2020; American Psychiatric Association, 2013; Dougherty et al., 2018; Stein et al., 2019). Remarkably, most of the OCD patients have a clear insight into their obsessive-compulsive (OC) behavior, but they fail to control it (Robbins et al., 2019; Stein et al., 2019). Common comorbidities include major depressive disorder, anxiety disorders, and substance use disorders (Alemany-Navarro et al., 2020; Stein et al., 2019). The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989) and the Obsessive-Compulsive Inventory-Revised (OCI-R) (Abramowitz & Deacon, 2006; Foa et al., 2002) are validated psychometric instruments to assess the severity and symptomatic dimensions of OCD.

The recommended first-line treatments for OCD are cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) medication. CBT incorporates cognitive therapy and exposure-

response prevention (ERP). ERP consists of the repetitive exposure to fearful stimuli with subsequent inhibition of compulsive behavior. Cognitive therapy mainly targets dysfunctional beliefs. As suggested by the name, SSRIs increased the serotonin levels by blocking its uptake. SSRIs also impact dopaminergic and glutamatergic transmission (Dougherty et al., 2018; Robbins et al., 2019; Stein et al., 2019). A full response to treatment occurs with a reduction of 35 % in the Y-BOCS scale (Kühne et al., 2020; Mataix-Cols et al., 2016). Approximately 30 to 60% of the patients are resistant to first-line treatments (Grassi & Pallanti, 2018; Hazari et al., 2016). Dose augmentation or the combination with a different antidepressant (e.g. tricyclic), antipsychotic, and glutamatergic medication might be used for refractory cases (Stein et al., 2019; Veale et al., 2014; Zhou et al., 2019). Invasive approaches such as deep-brain stimulation (Vicheva et al., 2020) and ablative neurosurgery (Lv et al., 2020) are used for the most severe cases. At the moment, non-invasive neurostimulation techniques are also being applied (e.g. repetitive and deep transcranial magnetic stimulation and transcranial direct-current stimulation) (Rapinesi et al., 2019).

Neuroimaging data has advanced the knowledge of OCD-related impairments in cortico-striato-thalamo-cortical circuits. Functional magnetic resonance imaging (fMRI) allows the measurement of blood-oxygenated-level-depend signals in brain regions activated during a task, and the functional correlations among brain regions at rest or during a task (functional connectivity) (Ugurbil, 2016). OCD is characterized by atrophy in prefrontal (anterior cingulate and ventromedial and dorsomedial prefrontal cortex [PFC]), insular and temporal regions, and hypertrophy in subcortical, cerebellar and occipitotemporal areas (Heuvel et al., 2020; Moreira et al., 2017; Maria Picó-Pérez et al., 2020). While performing affective tasks, OCD patients have enhanced brain response in PFC areas (medial PFC), anterior insula, and subcortical regions (amygdala, putamen, and thalamus) (Maria Picó-Pérez et al., 2020; Rasgon et al., 2017). Additionally, these patients present increased activity in dorsolateral PFC areas, posterior insula, and putamen, and decreased activity in the anterior cingulate, caudate, and visual regions during tasks involving executive functioning (Nakao et al., 2014; Maria Picó-Pérez et al., 2020; Rasgon et al., 2017). Alterations in frontolimbic, frontostriatal, frontoparietal, and cerebellar networks are also described in OCD (Heuvel et al., 2020; Moreira et al., 2017; Stein et al., 2019). Thus, OCD is defined by alterations in brain pathways underlying the processing of sensorimotor, motivational, cognitive, and affective information (Stein et al., 2019).

OCD individuals have deficits in several aspects of executive functioning: impairments in response inhibition; reduced cognitive flexibility; exacerbated habitual-behavior and deficient goal-direct behavior; working memory deficits; increased performance monitoring (Dougherty et al., 2018; Gruner & Pittenger, 2017; Robbins et al., 2019; Stein et al., 2019). Moreover, OCD also impacts decision-making, cognitive

control, and reward valuation processes (Dougherty et al., 2018; Gruner & Pittenger, 2017; Stein et al., 2019). Additionally, OCD patients have a dysfunctional understanding of their thoughts, including responsibility exacerbation, threat overestimation, uncertainty intolerance, and need for control (García-Soriano & Belloch, 2013; Hezel & McNally, 2016).

2. Obsessive-compulsive disorder and stress

Stress is defined by the response to environmental demands such as psychological or physical events called "stressors" that disturb our homeostasis. The stress response involves the activation of the autonomic nervous system with subsequent increases in metabolic function, blood pressure, and heart and respiration rates. The hypothalamic-pituitary-adrenal axis is also activated leading to the augmentation of cortisol levels. Also, the brain function in the hippocampus, amygdala, and PFC incorporates the response to stress demands. Besides the physiological response to stress, the exposure to stressors also triggers behavioral responses namely increased vigilance and cognitive control states to cope with the situation (de Kloet et al., 2005; Lucassen et al., 2014; N. Sousa, 2016; Nuno Sousa & Almeida, 2012). Psychological stress levels can be evaluated with the Perceived Stress Scale (PSS-10; 10 items) (S. Cohen et al., 1983).

Despite the adaptive and beneficial effects of stress, early-life, disproportionate, or prolonged stress responses are known as a susceptibility factor for psychiatric disorders. Patients with depression and post-traumatic stress disorder present altered cortisol levels (de Kloet et al., 2005; Musazzi et al., 2018; Pervanidou & Chrousos, 2018). OCD severity may be exacerbated by exposure to stressful environments and its onset may be linked to traumatic and stressful life events (e.g. changes in family and social relationships, socioeconomic problems, emotional or physical abuse, and health issues) (Adams et al., 2018; Coles et al., 2011; Raposo-Lima & Morgado, 2019; Eva Real et al., 2011). Approximately 25 to 70% of OCD patients report that their disorder onset is linked with stressful life events (Adams et al., 2018). Additionally, the chronic course of OCD results from an interplay between the genetic background and the occurrence of stressful life events (Ximena Goldberg et al., 2015; E. Real et al., 2013). Moreover, poorer treatment responses in OCD patients are associated with a history of trauma (Raposo-Lima & Morgado, 2019).

OCD is characterized by obsessive thoughts that are perceived by the patients as highly distressing (Adams et al., 2018). Furthermore, OCD severity is associated with psychological stress and cortisol levels (Melia et al., 2019; P. Morgado et al., 2013; Sousa-Lima et al., 2019). Moreover, common

anatomical and functional alterations in the striatum, hippocampus, amygdala, and PFC regions are reported after stress exposure and also in OCD individuals (Adams et al., 2018; de Kloet et al., 2005; Raposo-Lima & Morgado, 2019). Also, OCD patients exposed to stressful life events differ in terms of brain structure from patients without this exposure (E. Real et al., 2016). Animal and human studies demonstrated that both stress exposure and OCD are known to promote habitual behavior in detriment of goal-directed behavior. These behavioral alterations induce hypertrophy of the putamen and amygdala, and atrophy of the caudate and medial and orbitofrontal PFC regions (Adams et al., 2018; Raposo-Lima & Morgado, 2019). Moreover, impairments in reward sensitivity, response inhibition, attentional shifting, and decision-making are typical in chronic stress and OCD (Raposo-Lima & Morgado, 2019). Thus, OCD is a disorder sensitive to stress but the link between stress and OCD mechanisms is still poorly understood.

3. Cognitive regulation

Cognitive regulation refers to the adaptive self-regulation of cognitive processes to reach a goal. These cognitive processes may involve thoughts, beliefs, and emotion/affective information. When cognitive regulation corresponds to the self-regulation of emotions is denominated emotion regulation (Nigg, 2017). Thus, emotion regulation consists of controlling the experiencing and timing of emotions to achieve a desirable emotional state, by identifying emotions and selecting, implementing, and maintaining adequate regulation strategies (Ochsner et al., 2012; Pruessner et al., 2020; Sheppes et al., 2015).

The mechanisms of cognitive regulation develop throughout life and overlap with executive functioning abilities (e.g. working memory, attentional set-shifting, and response inhibition) (Amidfar et al., 2019; Langner et al., 2018; Nigg, 2017; Pruessner et al., 2020). They involve bottom-up processes corresponding to automatic responses to external sensory stimuli in subcortical regions (amygdala and ventral striatum/ventral tegmental area). Top-down processes are then triggered to modulate the activity in subcortical regions (Brandl et al., 2019; Cutuli, 2014; Nigg, 2017; Ochsner et al., 2012). These processes include brain responses in the anterior cingulate cortex and the ventromedial, ventrolateral, and dorsolateral PFC cortices, and the engagement of frontoparietal and cingulo-opercular brain networks (Amidfar et al., 2019; Brandl et al., 2019; Cutuli, 2014; Langner et al., 2018; Nigg, 2017; Ochsner et al., 2012; Pruessner et al., 2020). Thus, the insular, lateral temporal, and inferior parietal cortices are also critical for cognitive regulation (Cocchi et al., 2013).

Emotion dysregulation incorporates difficulties across several steps of emotion regulation process: identification of the need to regulate; selection of appropriate strategies; implementation of the strategies; monitoring of the strategies effects over time (Sheppes et al., 2015). The most commonly reported emotion regulation strategies are cognitive reappraisal and expressive suppression. Reappraisal comprises the reinterpretation of an emotional situation with a novel perspective to change its meaning and impact. This strategy is applied before the complete establishment of the emotional response ("antecedent-focused strategy"). On the other hand, suppression is used when the emotional response has already progressed ("response-focused strategy") and consists of the inhibition or reduction of emotion-related behaviors (Cutuli, 2014; Langner et al., 2018; Ochsner et al., 2012). Thus, suppression modifies behaviors without decreasing emotion experiencing in contrast to reappraisal that reduces emotional experiences and behavioral expression. In this way, the long-term use of suppression strategies in the face of situations eliciting negative emotions is associated with avoidant, depressive, and anxious indicators (Cutuli, 2014). The habitual use of cognitive reappraisal and expressive suppression is usually evaluated with the self-reported Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003).

Impairments of emotion regulation are a hallmark of several psychiatric conditions (e.g. depression, anxiety disorders, addiction, and eating disorders) (Cutuli, 2014; Nigg, 2017; Maria Picó-Pérez et al., 2017). For example, anxiety disorders are characterized by exacerbated emotional responses to negative/threatening cues and by the replacement of beneficial strategies by maladaptive tactics involving attentional deployment (e.g. worry). Patients with depression also use detrimental strategies such as persistent rumination to attempt to cope with aversive emotions (Naragon-Gainey et al., 2017; Sheppes et al., 2015). OCD is also associated with emotion regulation deficits, namely the frequent use of detrimental suppression strategies to decrease the distress elicited by intrusive thoughts, and the difficulty in using cognitive reappraisal to regulate emotions (Fink et al., 2018; Hezel & McNally, 2016). However, these deficits are still not well characterized.

OCD is also defined by an imbalance between cognitive flexibility and reward pathways that explains the execution of rewarding compulsive actions in response to uncontrollable obsessional thoughts (Albertella et al., 2020; Dougherty et al., 2018; Gruner & Pittenger, 2017). However, the mechanisms of cognitive control of reward processing are not yet understood in OCD. The cognitive regulation of rewards typically involves the regulation of craving for hedonic cues (e.g. food, sex, money, and drugs) (Brandl et al., 2019; Sun & Kober, 2020). The brain pathways of cognitive regulation of rewards overlap with the ones responsible for regulating emotions (Brandl et al., 2019; Ochsner et al., 2012; Sun & Kober, 2020). Indeed, both emotion and reward regulation rely on the selection and maintenance of an adequate

strategy accordingly to the valuation of the stimulus and the desired goal (Langner et al., 2018; Sheppes et al., 2015; Sun & Kober, 2020). For example, we might need to regulate anger when fighting with a friend or regulate our desire to eat unhealthy appetizing food. Typical strategies to cognitively regulate craving include cognitive reappraisal (focusing on positive feelings related to food/drug consumption or negative long-term consequences of this consumption) (Sun & Kober, 2020), suppression, and attentional deployment strategies (e.g. distraction) (Wolz et al., 2020). **Figure 1** illustrates the brain regions underlying cognitive regulation and their respective functions. Moreover, it represents the main differences between the regulation of emotions and rewards.

Depression, anxiety, post-traumatic stress disorder, and OCD are defined by general distress that might arise from persistent negative thoughts (e.g. rumination, worry, and obsessions) (Lucassen et al., 2014; Renna et al., 2020; Yap et al., 2018). The individuals suffering from these disorders and chronic stress are more prone to substance abuse and unhealthy diets (Renna et al., 2020; Nuno Sousa & Almeida, 2012). Moreover, stress and negative emotions influence the craving for food cues (Sun & Kober, 2020). An effective stress response requires the activation of motivational, attentional shifting/maintenance, and cognitive regulation and flexibility circuits that overlap with cognitive regulation pathways (Renna et al., 2020). Indeed, Herzberg and colleagues recently reviewed the impact of early life stressors on emotion and reward-processing, pointing to reductions in sensitivity to rewards and aversive/affective stimuli and alterations in cognitive regulation circuits (Herzberg & Gunnar, 2020). Considering that stress seems to aggravate OCD symptomology, stress levels may play a crucial role in the mechanisms of cognitive regulation in this disorder.

Nowadays several therapy-based approaches are applied to tackle emotion regulation dysfunctions, for example, cognitive-behavioral therapy, emotion regulation therapy, and affect regulation therapy (Renna et al., 2020; Sheppes et al., 2015). Recent developments in the neuroimaging and neuromodulation fields created the opportunity to link treatments focused on emotion regulation and brain activity (Amidfar et al., 2019; Linhartová et al., 2019). In particular, the neurofeedback technique allows the simultaneous regulation of emotional states and neural responses in regions associated with symptomatic manifestations. During fMRI neurofeedback, the activity of a specific brain region is measured in real-time while the fMRI images are being acquired. The activity signals are converted to visual/auditory feedback to the participant so he/she can cognitively or behaviorally modulate the brain activity into a desirable state (Watanabe et al., 2017). Distinct emotion regulation strategies (e.g. relaxation, recall of positive memories, or reappraisal) may be applied for neural modulation accordingly to the neurofeedback purpose (Linhartová et al., 2019). Despite the current applications of neurofeedback

to improve symptoms in psychiatric disorders (Dudek & Dodell-Feder, 2020), the efficacy of this technique in OCD remains poorly explored (Buyukturkoglu et al., 2015; Rance et al., 2018; Dustin Scheinost et al., 2014). Additionally, there is a lack of knowledge about the brain mechanisms targeted during neurofeedback, particularly for psychiatric conditions (Emmert et al., 2016; Linhartová et al., 2019).

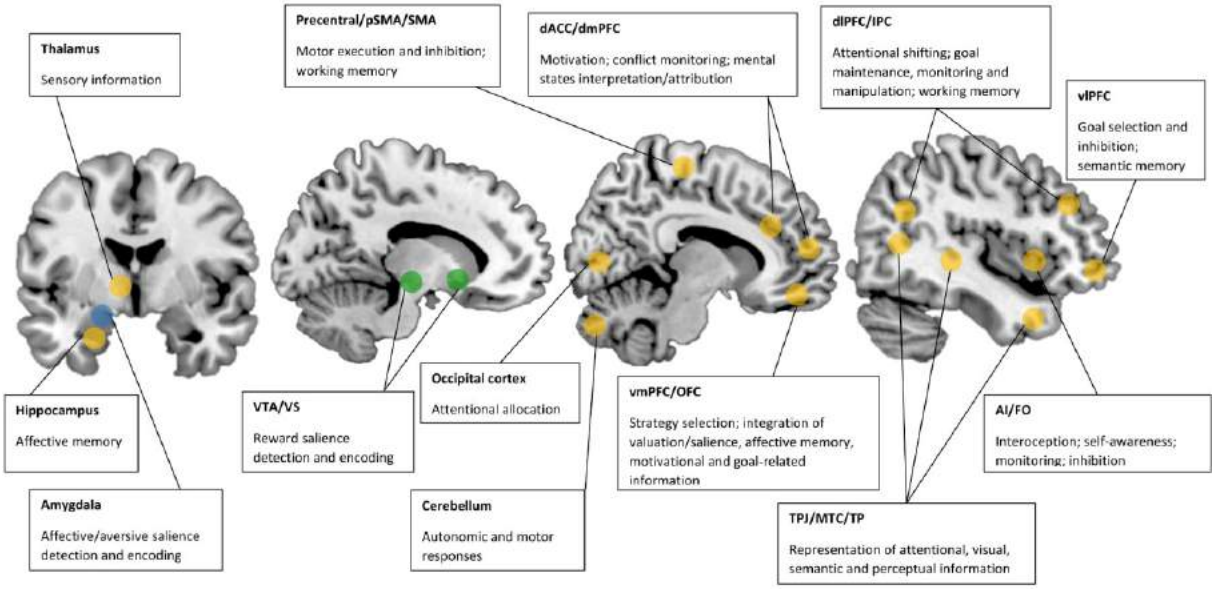


Figure 1 Representation of the brain regions underlying cognitive regulation processes and their respective functions. Yellow color represents regions involved in both emotion and reward regulation, while blue and green colors represent areas more frequently associated with emotion and reward processing, respectively (Amidfar et al., 2019; Brandl et al., 2019; Cocchi et al., 2013; Cutuli, 2014; Langner et al., 2018; Ochsner et al., 2012; Maria Picó-Pérez et al., 2017). The figure was created with MRIcron templates (https://people.cas.sc.edu/rorden/mricron/). The regions were drawn for illustrative purposes and do not represent the exact anatomical location. pSMA – pre-supplementary motor area; SMA – supplementary motor area; dACC – dorsal anterior cingulate cortex; dmPFC – dorsomedial prefrontal cortex; dlPFC – dorsolateral prefrontal cortex; IPC – inferior parietal cortex; vlPFC – ventrolateral prefrontal cortex; VTA – ventral tegmental area; VS – ventral striatum; vmPFC – ventromedial prefrontal cortex; OFC – orbitofrontal cortex; TPJ – temporoparietal junction; MTC – middle temporal cortex; TP – temporal pole; AI – anterior insula; FO – frontal operculum.

4. Aims

In this thesis, we intended to broaden the knowledge of the mechanisms of cognitive regulation of emotion and reward in OCD while also considering the impact of stress on these mechanisms. We defined the following aims:

- review the overall impairments in the mechanisms of cognitive regulation in OCD;
- characterize the impact of stress and OCD on cognitive regulation of emotion;
- study alterations in cognitive regulation of reward in chronic stress;
- explore deficits in cognitive regulation of reward in OCD;
- study the efficacy of neurofeedback as an emotion-regulation treatment in OCD.

5. Chapters overview

This thesis was organized into six chapters.

In **Chapter I,** we systematically reviewed the literature exploring cognitive regulation deficits in OCD, focusing on behavioral, physiological, and neurobiological variables.

In **Chapter II**, we studied the impact of obsessive-compulsive and stress symptoms on emotion-regulation in a sample of OCD patients and non-psychiatric participants using psychometric measurements.

In **Chapter III**, we conducted an experiment of cognitive regulation of reward processing in chronic stress. We used an fMRI task where chronically stressed students and students under regular activities had to cognitively upregulate or downregulate their craving before valuating food items. We evaluated changes in brain activity and valuation-related behavioral outcomes during the task.

In **Chapter IV**, we describe a study of cognitive regulation of reward processing in OCD. We applied the same fMRI task of **Chapter III** with non-psychiatric and OCD participants. We evaluated changes in brain activity and functional connectivity, and behavioral measures of valuation during the task.

In **Chapter V**, we investigated the efficacy of neurofeedback to reduce OCD symptoms by performing a systematic review and meta-analysis of the literature.

In **Chapter VI**, we report the preliminary findings of an fMRI neurofeedback protocol for treatment-resistant OCD patients with contamination/cleaning symptoms. We analyzed changes in psychometric variables as well as alterations of brain activity and functional connectivity after neurofeedback.

Figure 2 represents the associations among the main themes addressed in each chapter.

To finish, we discussed our main findings and provided directions for future research on the last section of the thesis.

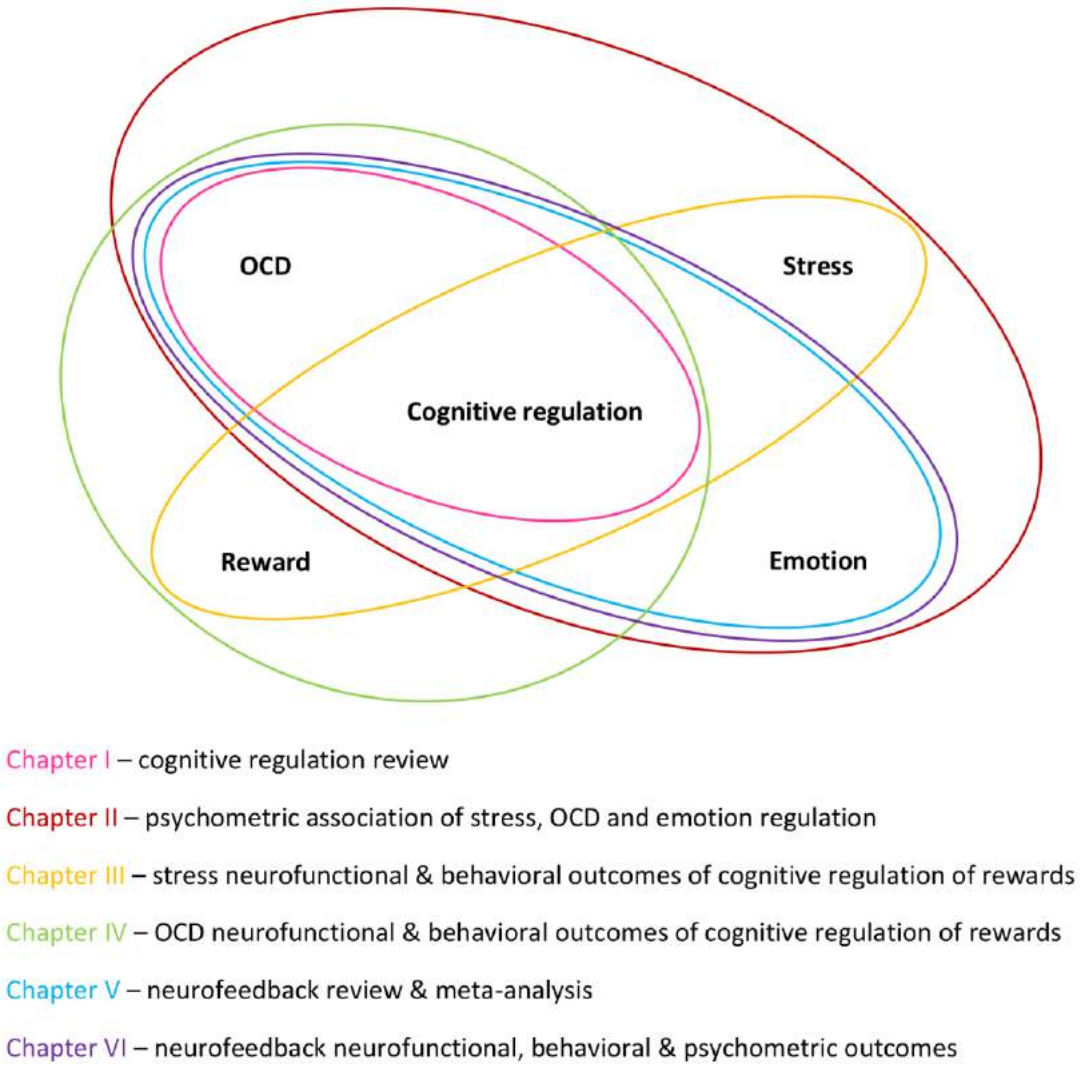


Figure 2 Representation of the main organization of the chapters.

6. References

Abramowitz, J. S., & Deacon, B. J. (2006). Psychometric properties and construct validity of the Obsessive–Compulsive Inventory—Revised: Replication and extension with a clinical sample. Journal of Anxiety Disorders, 20(8), 1016–1035. https://doi.org/10.1016/J.JANXDIS.2006.03.001

Adams, T. G., Kelmendi, B., Brake, C. A., Gruner, P., Badour, C. L., & Pittenger, C. (2018). The Role of Stress in the Pathogenesis and Maintenance of Obsessive-Compulsive Disorder. Chronic Stress, 2(1), 247054701875804. https://doi.org/10.1177/2470547018758043

Albertella, L., Le Pelley, M. E., Chamberlain, S. R., Westbrook, F., Lee, R. S. C., Fontenelle, L. F., Grant, J. E., Segrave, R., McTavish, E., & Yücel, M. (2020). Reward-related attentional capture and cognitive inflexibility interact to determine greater severity of compulsivity-related problems. Journal of Behavior Therapy and Experimental Psychiatry, 101580. https://doi.org/10.1016/j.jbtep.2020.101580

Alemany-Navarro, M., Cruz, R., Real, E., Segalàs, C., Bertolín, S., Rabionet, R., Carracedo, Á., Menchón, J. M., & Alonso, P. (2020). Looking into the genetic bases of OCD dimensions: a pilot genome-wide association study. Translational Psychiatry, 10(1), 151. https://doi.org/10.1038/s41398-020-0804-z

American Psychiatric Association. (2013). Diagnostic Statistical Manual of Mental Disorders (DSM-5). In American Psychiatric Association (5th, revised ed.). American Psychiatric Association Pub, 2013.

Amidfar, M., Ko, Y.-H., & Kim, Y.-K. (2019). Neuromodulation and Cognitive Control of Emotion (pp. 545–564). https://doi.org/10.1007/978-981-32-9721-0_27

Brandl, F., Le Houcq Corbi, Z., Mulej Bratec, S., & Sorg, C. (2019). Cognitive reward control recruits medial and lateral frontal cortices, which are also involved in cognitive emotion regulation: A coordinate-based meta-analysis of fMRI studies. NeuroImage, 200(August 2018), 659–673. https://doi.org/10.1016/j.neuroimage.2019.07.008

Buyukturkoglu, K., Roettgers, H., Sommer, J., Rana, M., Dietzsch, L., Arikan, E. B., Veit, R., Malekshahi, R., Kircher, T., Birbaumer, N., Sitaram, R., & Ruiz, S. (2015). Self-Regulation of Anterior Insula with Real-Time fMRI and Its Behavioral Effects in Obsessive-Compulsive Disorder: A Feasibility Study. PLOS ONE, 10(8), e0135872. https://doi.org/10.1371/journal.pone.0135872

Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. Trends in Cognitive Sciences, 17(10), 493–501. https://doi.org/10.1016/j.tics.2013.08.006

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A Global Measure of Perceived Stress. Journal of Health and Social Behavior, 24(4), 385. https://doi.org/10.2307/2136404

Coles, M. E., Johnson, E. M., & Schubert, J. R. (2011). Retrospective Reports of the Development of Obsessive Compulsive Disorder: Extending Knowledge of the Protracted Symptom Phase. Behavioural and Cognitive Psychotherapy, 39(5), 579–589. https://doi.org/10.1017/S135246581100004X

Cutuli, D. (2014). Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Frontiers in Systems Neuroscience, 8(September), 1–6. https://doi.org/10.3389/fnsys.2014.00175

de Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: from adaptation to disease. Nature Reviews Neuroscience, 6(6), 463–475. https://doi.org/10.1038/nrn1683

Dougherty, D. D., Brennan, B. P., Stewart, S. E., Wilhelm, S., Widge, A. S., & Rauch, S. L. (2018). Neuroscientifically Informed Formulation and Treatment Planning for Patients With Obsessive-Compulsive Disorder. JAMA Psychiatry, 75(10), 1081. https://doi.org/10.1001/jamapsychiatry.2018.0930

Dudek, E., Dodell-Feder, D., 2020. The efficacy of real-time functional magnetic resonance imaging neurofeedback for psychiatric illness: A meta-analysis of brain and behavioral outcomes. PsyArXiv Prepr. 104–108. https://doi.org/10.31234/osf.io/ensr9

Emmert, K., Kopel, R., Sulzer, J., Brühl, A. B., Berman, B. D., Linden, D. E. J., Horovitz, S. G., Breimhorst, M., Caria, A., Frank, S., Johnston, S., Long, Z., Paret, C., Robineau, F., Veit, R., Bartsch, A., Beckmann, C. F., Van De Ville, D., & Haller, S. (2016). Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated? NeuroImage, 124, 806–812. https://doi.org/10.1016/j.neuroimage.2015.09.042

Fink, J., Pflugradt, E., Stierle, C., & Exner, C. (2018). Changing disgust through imagery rescripting and cognitive reappraisal in contamination-based obsessive-compulsive disorder. Journal of Anxiety Disorders, 54(January), 36–48. https://doi.org/10.1016/j.janxdis.2018.01.002

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. Psychological Assessment, 14(4), 485–496. https://doi.org/10.1037/1040-3590.14.4.485

García-Soriano, G., & Belloch, A. (2013). Symptom dimensions in obsessive-compulsive disorder: Differences in distress, interference, appraisals and neutralizing strategies. Journal of Behavior Therapy and Experimental Psychiatry, 44(4), 441–448. https://doi.org/10.1016/j.jbtep.2013.05.005

Goldberg, X., Soriano-Mas, C., Alonso, P., Segalàs, C., Real, E., López-Solà, C., Subirà, M., Via, E., Jiménez-Murcia, S., Menchón, J. M., & Cardoner, N. (2015). Predictive value of familiality, stressful life events and gender on the course of obsessive-compulsive disorder. Journal of Affective Disorders, 185, 129–134. https://doi.org/10.1016/j.jad.2015.06.047

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. II. Validity. Archives of General Psychiatry, 46(11), 1012–1016. http://www.ncbi.nlm.nih.gov/pubmed/2510699

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Archives of General Psychiatry, 46(11), 1006–1011. http://www.ncbi.nlm.nih.gov/pubmed/2684084

Grassi, G., & Pallanti, S. (2018). Current and up-and-coming pharmacotherapy for obsessive-compulsive disorder in adults. In Expert Opinion on Pharmacotherapy (Vol. 19, Issue 14, pp. 1541–1550). Taylor and Francis Ltd. https://doi.org/10.1080/14656566.2018.1528230

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. Journal of Personality and Social Psychology, 85(2), 348–362. http://www.ncbi.nlm.nih.gov/pubmed/12916575

Gruner, P., & Pittenger, C. (2017). Cognitive inflexibility in Obsessive-Compulsive Disorder. Neuroscience, 345(August), 243–255. https://doi.org/10.1016/j.neuroscience.2016.07.030

Hazari, N., Narayanaswamy, J. C., & Arumugham, S. S. (2016). Predictors of response to serotonin reuptake inhibitors in obsessive-compulsive disorder. Expert Review of Neurotherapeutics, 16(10), 1175–1191. https://doi.org/10.1080/14737175.2016.1199960

Herzberg, M. P., & Gunnar, M. R. (2020). Early life stress and brain function: Activity and connectivity associated with processing emotion and reward. NeuroImage, 209(June 2019), 116493. https://doi.org/10.1016/j.neuroimage.2019.116493

Heuvel, O. A., Boedhoe, P. S. W., Bertolin, S., Bruin, W. B., Francks, C., Ivanov, I., Jahanshad, N., Kong, X., Kwon, J. S., O'Neill, J., Paus, T., Patel, Y., Piras, F., Schmaal, L., Soriano-Mas, C., Spalletta, G., Wingen, G. A., Yun, J., Vriend, C., … Stein, D. J. (2020). An overview of the first 5 years of the ENIGMA obsessive–compulsive disorder working group: The power of worldwide collaboration. Human Brain Mapping, February, hbm.24972. https://doi.org/10.1002/hbm.24972

Hezel, D. M., & McNally, R. J. (2016). A Theoretical review of cognitive biases and deficits in obsessive–compulsive disorder. Biological Psychology, 121, 221–232. https://doi.org/10.1016/j.biopsycho.2015.10.012

Kühne, F., Ay, D. S., Marschner, L., & Weck, F. (2020). The heterogeneous course of OCD – A scoping review on the variety of definitions. Psychiatry Research, 285(January), 112821. https://doi.org/10.1016/j.psychres.2020.112821

Langner, R., Leiberg, S., Hoffstaedter, F., & Eickhoff, S. B. (2018). Towards a human self-regulation system: Common and distinct neural signatures of emotional and behavioural control. Neuroscience & Biobehavioral Reviews, 90(1), 400–410. https://doi.org/10.1016/j.neubiorev.2018.04.022

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. NeuroImage, 193(March), 75–92. https://doi.org/10.1016/j.neuroimage.2019.03.011

Lucassen, P. J., Pruessner, J., Sousa, N., Almeida, O. F. X., Van Dam, A. M., Rajkowska, G., Swaab, D. F., & Czéh, B. (2014). Neuropathology of stress. Acta Neuropathologica, 127(1), 109–135. https://doi.org/10.1007/s00401-013-1223-5

Lv, Q., Lv, Q., Yin, D., Zhang, C., Sun, B., Voon, V., & Wang, Z. (2020). Neuroanatomical Substrates and Predictors of Response to Capsulotomy in Intractable Obsessive-Compulsive Disorder. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. https://doi.org/10.1016/j.bpsc.2020.05.005

Mataix-Cols, D., de la Cruz, L. F., Nordsletten, A. E., Lenhard, F., Isomura, K., & Simpson, H. B. (2016). Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder. World Psychiatry, 15(1), 80–81. https://doi.org/10.1002/wps.20299

Melia, C. S., Soria, V., Salvat-Pujol, N., Cabezas, Á., Nadal, R., Urretavizcaya, M., Gutiérrez-Zotes, A., Monreal, J. A., Crespo, J. M., Alonso, P., Vilella, E., Palao, D., Menchón, J. M., & Labad, J. (2019). Sex-specific association between the cortisol awakening response and obsessive-compulsive symptoms in healthy individuals. Biology of Sex Differences, 10(1), 55. https://doi.org/10.1186/s13293-019-0273-3

Moreira, P. S., Marques, P., Soriano-Mas, C., Magalhães, R., Sousa, N., Soares, J. M., & Morgado, P. (2017). The neural correlates of obsessive-compulsive disorder: a multimodal perspective. Translational Psychiatry, 7(8), e1224. https://doi.org/10.1038/tp.2017.189

Morgado, P., Freitas, D., Bessa, J. M., Sousa, N., & Cerqueira, J. J. (2013). Perceived Stress in Obsessive–Compulsive Disorder is Related with Obsessive but Not Compulsive Symptoms. Frontiers in Psychiatry, 4(APR), 21. https://doi.org/10.3389/fpsyt.2013.00021

Musazzi, L., Tornese, P., Sala, N., & Popoli, M. (2018). What Acute Stress Protocols Can Tell Us About PTSD and Stress-Related Neuropsychiatric Disorders. Frontiers in Pharmacology, 9(JUN), 1–13. https://doi.org/10.3389/fphar.2018.00758

Nakao, T., Okada, K., & Kanba, S. (2014). Neurobiological model of obsessive-compulsive disorder: Evidence from recent neuropsychological and neuroimaging findings. Psychiatry and Clinical Neurosciences, 68(8), 587–605. https://doi.org/10.1111/pcn.12195

Naragon-Gainey, K., McMahon, T. P., & Chacko, T. P. (2017). The structure of common emotion regulation strategies: A meta-analytic examination. Psychological Bulletin, 143(4), 384–427. https://doi.org/10.1037/bul0000093

Nigg, J. T. (2017). Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. Journal of Child Psychology and Psychiatry, 58(4), 361–383. https://doi.org/10.1111/jcpp.12675

Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Annals of the New York Academy of Sciences, 1251(1), E1–E24. https://doi.org/10.1111/j.1749-6632.2012.06751.x

Pervanidou, P., & Chrousos, G. P. (2018). Early-Life Stress: From Neuroendocrine Mechanisms to Stress-Related Disorders. Hormone Research in Paediatrics, 89(5), 372–379. https://doi.org/10.1159/000488468

Picó-Pérez, M., Moreira, P. S., Ferreira, V. D. M., Radua, J., Mataix-Cols, D., Sousa, N., Soriano-Mas, C., & Morgado, P. (2020). Modality-specific overlaps in brain structure and function in Obsessive-compulsive disorder: multimodal meta-analysis of case-control MRI studies. Neuroscience & Biobehavioral Reviews. https://doi.org/10.1016/j.neubiorev.2020.01.033

Picó-Pérez, M., Radua, J., Steward, T., Menchón, J. M., & Soriano-Mas, C. (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 79(January), 96–104. https://doi.org/10.1016/j.pnpbp.2017.06.001

Pruessner, L., Barnow, S., Holt, D. V., Joormann, J., & Schulze, K. (2020). A cognitive control framework for understanding emotion regulation flexibility. Emotion, 20(1), 21–29. https://doi.org/10.1037/emo0000658

Rance, M., Walsh, C., Sukhodolsky, D. G., Pittman, B., Qiu, M., Kichuk, S. A., Wasylink, S., Koller, W. N., Bloch, M., Gruner, P., Scheinost, D., Pittenger, C., & Hampson, M. (2018). Time course of clinical change following neurofeedback. NeuroImage. https://doi.org/10.1016/j.neuroimage.2018.05.001

Rapinesi, C., Kotzalidis, G. D., Ferracuti, S., Sani, G., Girardi, P., & Del Casale, A. (2019). Brain Stimulation in Obsessive-Compulsive Disorder (OCD): A Systematic Review. Current Neuropharmacology, 17(8), 787–807. https://doi.org/10.2174/1570159X17666190409142555

Raposo-Lima, C., & Morgado, P. (2019). The Role of Environmental Factors in the Pathogenesis of Obsessive-Compulsive and Related Disorders. In F. L. Fontenelle & M. Yucel (Eds.), A Transdiagnostic Approach to Obsessions, Compulsions and Related Phenomena (p. 452). Cambridge University Press. https://books.google.pt/books?id=Zqh7DwAAQBAJ&pg=PA39&lpg=PA39&dq=catarina+lima+chapter+stress+obsessive&source=bl&ots=ZPksw8byc0&sig=ACfU3U3gYzgf9NnKCS9f9XgeqkwwNahPkA&hl=pt-PT&sa=X&ved=2ahUKEwijpKW394jqAhUMqxoKHcCID0kQ6AEwAHoECAoQAQ#v=onepage&q=catarina

Rasgon, A., Lee, W. H., Leibu, E., Laird, A., Glahn, D., Goodman, W., & Frangou, S. (2017). Neural correlates of affective and non-affective cognition in obsessive compulsive disorder: A meta-analysis of functional imaging studies. European Psychiatry, 46, 25–32. https://doi.org/10.1016/j.eurpsy.2017.08.001

Real, E., Gratacòs, M., Labad, J., Alonso, P., Escaramís, G., Segalàs, C., Subirà, M., López-Solà, C., Estivill, X., & Menchón, J. M. (2013). Interaction of SLC1A1 gene variants and life stress on pharmacological resistance in obsessive–compulsive disorder. The Pharmacogenomics Journal, 13(5), 470–475. https://doi.org/10.1038/tpj.2012.30

Real, E., Subirà, M., Alonso, P., Segalàs, C., Labad, J., Orfila, C., López-Solà, C., Martínez-Zalacaín, I., Via, E., Cardoner, N., Jiménez-Murcia, S., Soriano-Mas, C., & Menchón, J. M. (2016). Brain structural correlates of obsessive–compulsive disorder with and without preceding stressful life events. The World Journal of Biological Psychiatry, 17(5), 366–377. https://doi.org/10.3109/15622975.2016.1142606

Real, Eva, Labad, J., Alonso, P., Segalàs, C., Jiménez-Murcia, S., Bueno, B., Subirà, M., Vallejo, J., & Menchón, J. M. (2011). Stressful life events at onset of obsessive-compulsive disorder are associated with a distinct clinical pattern. Depression and Anxiety, 28(5), 367–376. https://doi.org/10.1002/da.20792

Renna, M. E., Fresco, D. M., & Mennin, D. S. (2020). Emotion Regulation Therapy and Its Potential Role in the Treatment of Chronic Stress-Related Pathology Across Disorders. Chronic Stress, 4, 247054702090578. https://doi.org/10.1177/2470547020905787

Robbins, T. W., Vaghi, M. M., & Banca, P. (2019). Obsessive-Compulsive Disorder: Puzzles and Prospects. Neuron, 102(1), 27–47. https://doi.org/10.1016/j.neuron.2019.01.046

Scheinost, D., Stoica, T., Wasylink, S., Gruner, P., Saksa, J., Pittenger, C., & Hampson, M. (2014). Resting state functional connectivity predicts neurofeedback response. Frontiers in Behavioral Neuroscience, 8(SEP), 338. https://doi.org/10.3389/fnbeh.2014.00338

Sheppes, G., Suri, G., & Gross, J. J. (2015). Emotion Regulation and Psychopathology. Annual Review of Clinical Psychology, 11(1), 379–405. https://doi.org/10.1146/annurev-clinpsy-032814-112739

Sousa-Lima, J., Moreira, P. S., Raposo-Lima, C., Sousa, N., & Morgado, P. (2019). Relationship between obsessive compulsive disorder and cortisol: Systematic review and meta-analysis. European Neuropsychopharmacology, 29(11), 1185–1198. https://doi.org/10.1016/j.euroneuro.2019.09.001

Sousa, N. (2016). The dynamics of the stress neuromatrix. Molecular Psychiatry, 21(3), 302–312. https://doi.org/10.1038/mp.2015.196

Sousa, Nuno, & Almeida, O. F. X. (2012). Disconnection and reconnection: the morphological basis of (mal)adaptation to stress. Trends in Neurosciences, 35(12), 742–751. https://doi.org/10.1016/j.tins.2012.08.006

Stein, D. J., Costa, D. L. C., Lochner, C., Miguel, E. C., Reddy, Y. C. J., Shavitt, R. G., van den Heuvel, O. A., & Simpson, H. B. (2019). Obsessive–compulsive disorder. Nature Reviews Disease Primers, 5(1), 52. https://doi.org/10.1038/s41572-019-0102-3

Sun, W., & Kober, H. (2020). Regulating Food Craving: From Mechanisms to Interventions. Physiology & Behavior, 112878. https://doi.org/10.1016/j.physbeh.2020.112878

Ugurbil, K. (2016). What is feasible with imaging human brain function and connectivity using functional magnetic resonance imaging. Philosophical Transactions of the Royal Society B: Biological Sciences, 371(1705). https://doi.org/10.1098/rstb.2015.0361

Veale, D., Miles, S., Smallcombe, N., Ghezai, H., Goldacre, B., & Hodsoll, J. (2014). Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis. BMC Psychiatry, 14(1), 317. https://doi.org/10.1186/s12888-014-0317-5

Vicheva, P., Butler, M., & Shotbolt, P. (2020). Deep brain stimulation for obsessive-compulsive disorder: A systematic review of randomised controlled trials. Neuroscience & Biobehavioral Reviews, 109(January), 129–138. https://doi.org/10.1016/j.neubiorev.2020.01.007

Watanabe, T., Sasaki, Y., Shibata, K., & Kawato, M. (2017). Advances in fMRI Real-Time Neurofeedback. In Trends in Cognitive Sciences (Vol. 21, Issue 12, pp. 997–1010). Elsevier Ltd. https://doi.org/10.1016/j.tics.2017.09.010

Wolz, I., Nannt, J., & Svaldi, J. (2020). Laboratory-based interventions targeting food craving: A systematic review and meta-analysis. Obesity Reviews, 21(5), 1–15. https://doi.org/10.1111/obr.12996

Yap, K., Mogan, C., Moriarty, A., Dowling, N., Blair-West, S., Gelgec, C., & Moulding, R. (2018). Emotion regulation difficulties in obsessive-compulsive disorder. Journal of Clinical Psychology, 74(4), 695–709. https://doi.org/10.1002/jclp.22553

Zhou, D.-D., Zhou, X.-X., Li, Y., Zhang, K.-F., Lv, Z., Chen, X.-R., Wan, L.-Y., Wang, W., Wang, G.-M., Li, D.-Q., Ai, M., & Kuang, L. (2019). Augmentation agents to serotonin reuptake inhibitors for treatment-resistant obsessive-compulsive disorder: A network meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 90, 277–287. https://doi.org/10.1016/j.pnpbp.2018.12.009

CHAPTER I

A systematic review of behavioral, physiological, and neurobiological cognitive regulation alterations in obsessive-compulsive disorder

Sónia Ferreira, José Miguel Pêgo, Pedro Morgado

Manuscript submitted for publication

A systematic review of behavioral, physiological, and neurobiological cognitive regulation alterations in obsessive-compulsive disorder

Sónia Ferreira[1,2], José Miguel Pêgo[1,2], Pedro Morgado[1,2,3]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [2]ICVS-3Bs PT Government Associate Laboratory, Braga/Guimarães, Portugal; [3]Clinical Academic Center-Braga (2CA), Braga, Portugal

1. Abstract

Obsessive-compulsive disorder (OCD) is characterized by cognitive regulation deficits. However, the current literature has focused on executive functioning and emotional responses impairments in this disorder. Herein, we conducted a systematic review of studies assessing the behavioral, physiological, and neurobiological alterations in cognitive regulation in obsessive-compulsive patients using the PubMed database. Most of the studies included explored behavioral (distress, arousal, and frequency of intrusive thoughts) and neurobiological measures (brain activity and functional connectivity) using affective cognitive regulation paradigms. Our results pointed to the advantageous use of reappraisal and acceptance strategies in contrast to suppression to reduce distress and frequency of intrusive thoughts. Moreover, we observed alterations in frontoparietal network activity during cognitive regulation. Our conclusions are limited by the inclusion of studies with small samples and patients under treatment. Additionally, the search was only conducted in one database. Nonetheless, our findings support the OCD impairments in cognitive regulation of emotion and might help to improve current guidelines for cognitive therapy.

2. Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts (obsessions) and repetitive or ritualistic actions or mental acts intended to diminish the anxiety and distress elicited by obsessions (compulsions) (American Psychiatric Association, 2013). In addition to its distinctive symptoms, OCD is defined by cognitive deficits involving memory and attentional biases towards relevant/threatening stimuli, memory distrust, and difficulty in accessing internal states. Thus, these patients depend on external stimuli and reassurance (Hezel & McNally, 2016; Rasgon et al., 2017). The past literature has focused on the study of executive function in OCD patients, mainly by using memory, inhibition, attentional shifting, reversal learning, and interference tasks (Gruner & Pittenger, 2017; Maria Picó-Pérez et al., 2020; Rasgon et al., 2017). Given that OCD patients might be frequently focused on controlling or responding to their obsessions, they might have an overall impaired performance on executive tasks. They might lack the cognitive flexibility necessary for task performance because their resources are taken by obsessive thoughts (Gruner & Pittenger, 2017; Hallion et al., 2019; Kikul et al., 2011; Maria Picó-Pérez et al., 2020). Indeed, prior research showed evidence that cognitive flexibility deficits emerge in emotionally relevant contexts in OCD patients (Zetsche et al., 2015).

Earlier models of OCD proposed that obsessions and compulsions result from cognitive deficits in the interpretation of thoughts. OCD patients have dysfunctional beliefs of higher significance/need for control of thoughts, inflated responsibility, and overestimation of threat (García-Soriano & Belloch, 2013; Hezel & McNally, 2016; Morillo et al., 2007; Najmi et al., 2010; Purdon et al., 2005). Despite the augmented necessity to control thoughts, OCD individuals apply inadequate strategies that intensify their occurrence: compulsions, neutralizing, suppression, and worry (Ahern et al., 2015; García-Soriano & Belloch, 2013; Hezel & McNally, 2016; Morillo et al., 2007; Najmi et al., 2010; Salkovskis et al., 2003).

Cognitive regulation consists of the pliable modulation of cognition arbitrated by central and peripheral systems (Cocchi et al., 2013; Nigg, 2017). This regulation involves top-down/deliberate and bottom-up/automatic mechanisms. Top-down processes respond to internal mental representations (e.g. goals/rules) while bottom-up mechanisms are associated with response to external/sensory stimuli (Hallion et al., 2019; Nigg, 2017). The cingulo-opercular (ventrolateral prefrontal cortex [vlPFC], dorsal anterior cingulate cortex [ACC], and anterior insula) and frontoparietal (dorsolateral PFC [dlPFC], posterior/inferior parietal and inferior temporal cortices) networks are associated with cognitive regulation (Cocchi et al., 2013; Nigg, 2017). The frontoparietal network is responsible for allocation of attention, while the cingulo-opercular network adjusts goal-related information and processes salient stimuli (Cocchi

et al., 2013). These networks interact through connections with the thalamus, hippocampus, and cerebellum (Cocchi et al., 2013; Nigg, 2017). The cingulo-opercular network mediates the correlation between the frontoparietal and default-mode networks during rest and cognitive control tasks (Cocchi et al., 2013).

Despite some evidence of cognitive regulation impairments in OCD, there is a lack of research summarizing the previous findings. Previous authors have focused on reviewing executive functioning and emotion processing in OCD (Gruner & Pittenger, 2017; Maria Picó-Pérez et al., 2020; Rasgon et al., 2017; A. L. Thorsen et al., 2018). Herein, we systematically reviewed the past literature to elucidate the main cognitive regulation processes impacted by OCD. We focused on studies assessing objective behavioral, physiological, and neurobiological parameters and not subjective self-reported data such as psychometric scales (Webb et al., 2012).

3. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) norms (Liberati et al., 2009; Moher et al., 2009) for the systematic review. We searched PubMed (Medline) database on the 14th of April 2020 using the combination of the following terms: *(OCD OR "obsessive-compulsive disorder" OR "obsessive compulsive disorder") AND (regulation OR reappraisal OR control) AND cognitive*. We restricted the findings to articles in English, with human participants, with the availability of a full-text document, and reporting original results (reviews and book chapters were excluded). The author SF conducted the search and the eligibility assessment. The results were discussed among all authors in case of doubt. First, we selected the articles by the title and then by the abstract content. Later, the full text of the articles was analyzed accordingly to the inclusion criteria. The inclusion criteria were: (1) the existence of a control group with non-psychiatric participants (controls); (2) the existence of an OCD group with a clear clinical diagnosis; (3) the inclusion of a direct statistical comparison between the control and the OCD group; (4) the assessment of cognitive regulation with behavioral, physiological, or neurobiological measurements. The exclusion criterium was the sole use of self-reported measures of cognitive regulation (e.g. psychometric scales or questionnaires).

We extracted the following information from each article: (1) group characterization; (2) group size; (3) group mean age; (4) group gender ratio; (5) diagnosis instrument; (6) mean Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score; (7) treatment approaches; (8) psychometric characterization

related to cognitive regulation; (9) task description; (10) behavioral results; (10) physiological outcomes; (12) neurobiological findings, (12) techniques employed. Studies with common authors were carefully analyzed to avoid data duplication.

4. Results

Figure 1 represents the selection process. The search yielded a total of 1,198 studies and 19 articles were additionally identified through reference lists. No unpublished studies were found. After abstract reading, we selected 43 articles and we included 11 studies after full-text reading. Two studies used the same sample (De Wit et al., 2015; A. L. L. Thorsen et al., 2019) and one study had two experiments with distinct samples (Tolin, Abramowitz, Przeworski, et al., 2002) (one with an overlapping sample from another study (Tolin, Abramowitz, Hamlin, et al., 2002)). Thirty-two reports did not meet the study criteria: 12 articles only assessed self-reported measures of cognitive regulation; 10 articles did not explore cognitive regulation processes; 7 reports did not incorporate a healthy control group; 3 studies did not statistically compare OCD and control participants. The final selected articles were published between 1999 and 2019 by authors from the USA, Germany, The Netherlands, Sweden, Spain, Turkey, Norway, and South Africa.

The studies included 301 OCD patients and 254 healthy participants in total, with an average of 27.4 ± 17.6 patients (mean ± standard deviation) and 23.1 ± 11.2 control participants per study. The average age for OCD participants was 31.5 ± 3.8 years and 30.8 ± 5.1 years for controls. On average, 49.7 ± 8.1% of OCD patients and 54.4 ± 9.3% of controls were female. All OCD patients were diagnosed with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and had an average Y-BOCS total score of 22.4 ± 1.3 (one study with missing information). Five articles explored behavioral tasks (**Table 1**) and 6 studies evaluated neurobiological and/or behavioral processes with functional magnetic resonance imaging (fMRI) and electroencephalography (**Table 2**).

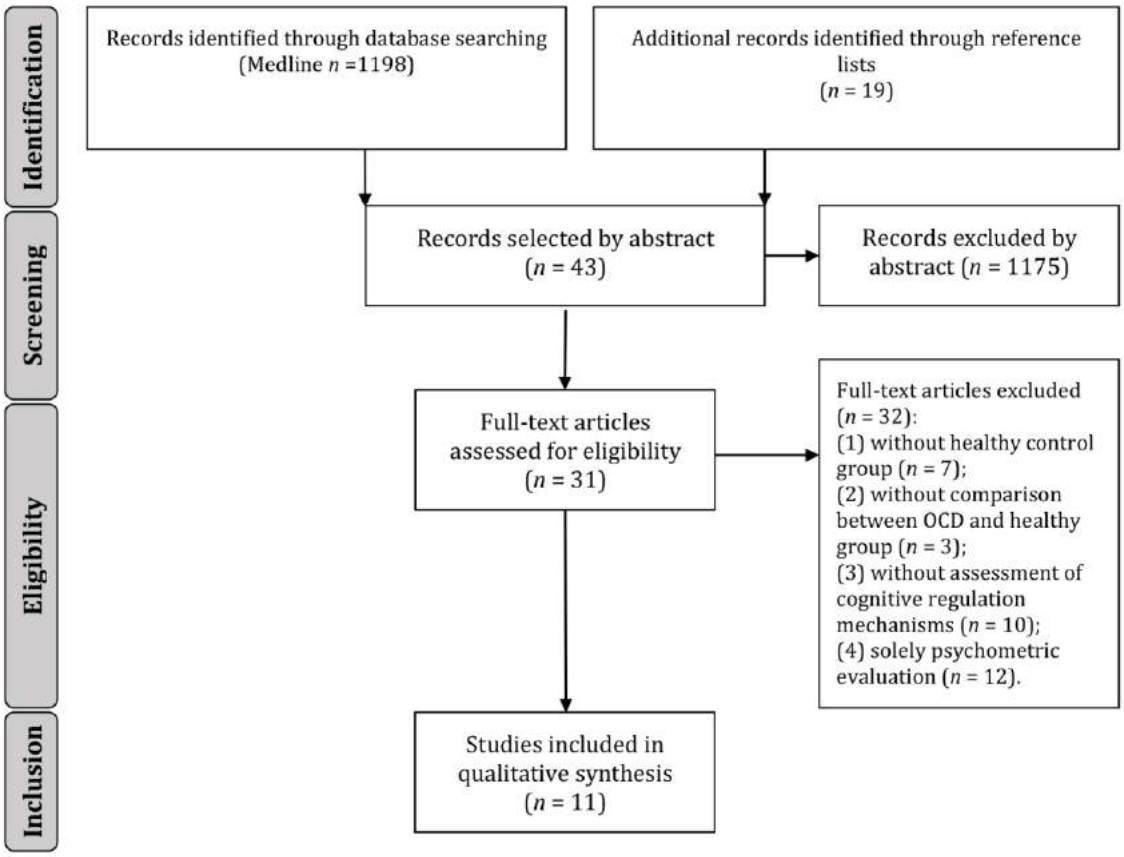


Figure 1 Flow diagram of the literature search [adapted from (Liberati et al., 2009; Moher et al., 2009)].

Table 1 Summary of the studies with behavioral measures of cognitive regulation. The psychometrics and results comprise direct statistical comparisons between groups (OCD vs. healthy).

Study	Groups	Size	Age (years)	Gender (%F | %M)	Diagnosis	Y-BOCS	Treatment	Psychometrics	Task	Results
Janeck et al. 1999	OCD	31	31.9 ± 10.2	39 | 61	DSM-IV	22.0 ± 6.3	48% medicated	-	Suppression of negative thought	↑overall frequency and distress from negative thought; ↑number of participants with negative thought after suppression.
	Healthy	32	31.2 ± 13.5	66 | 34		-	-			
Tolin et al. 2002b*	OCD	15	29.6 ± 9.9	50 | 50	DSM-IV	23.8 ± 5.4	67% medicated; 73% CBT	-	Suppression of neutral thought	↑frequency of target thought during suppression; ↑frequency and time thinking about target thought overall.
	Healthy	14	26.9 ± 6.5	43 | 57		-	-			
	OCD	15	25.8 ± 10.1	36 | 64	DSM-IV	24.2 ± 5.3	75% medicated; 75% CBT	-	Suppression of neutral thought	↓detection time for word related to target thought versus non-related words and non-words during suppression.
	Healthy	13	25.5 ± 6.0	61 | 39		-	-			
Tolin et al. 2002a*	OCD	17	29.6 ± 9.9	50 | 50	DSM-IV	23.8 ± 5.4	67% medicated; 73% CBT	-	Suppression of neutral thought	↑frequency of target thought during suppression; ↑internal meaning (weakness/uncontrollable thoughts) of suppression failure.
	Healthy	8	25.1 ± 4.8	37 | 63		-	-			
Najmi et al. 2009	OCD	20	29.0 ± 12.0	55 | 45	DSM-IV	obsessions 11.1 ± 3.1; compulsions 10.7 ± 4.7	95% medicated	-	Suppression, focused distraction, or acceptance of intrusive thoughts	↑distress during all conditions; ↑intrusive thoughts after and during suppression; ↑distress after versus during suppression; ↑distress after suppression versus focused distraction and acceptance; ↑intrusive thoughts after suppression versus acceptance; ↓distress after versus during acceptance.
	Healthy	20	30.0 ± 9.0	65 | 35		obsessions 1.5 ± 2.0; compulsions 1.0 ± 1.7	-			
Fink et al. 2018	OCD contamination/cleaning	30	33.3 ± 11.4	59 | 41	DSM-IV	23.0 ± 6.1	60% medicated	↓ERQ reappraisal and ↑ERQ suppression	Mental imagery rescripting or cognitive reappraisal of disgust-inducing pictures	↑disgust ratings before the task.
	Healthy	30	32.8 ± 11.9	59 | 41		-	-			

OCD – obsessive-compulsive disorder; F – female; M – male; Y-BOCS – Yale-Brown Obsessive Compulsive Scale; DSM - Diagnostic and Statistical Manual of Mental Disorders; CBT – cognitive-behavioral therapy; ERQ – Emotion Regulation Questionnaire. *Studies with overlapping samples.

Table 2 Summary of the studies with behavioral and/or neurobiological measures of cognitive regulation. The psychometrics and results comprise direct statistical comparisons between groups (OCD vs. healthy).

Study	Groups	Size	Age (years)	Gender (%F | %M)	Diagnosis	Y-BOCS	Treatment	Psychometrics	Technique	Task	Behavioral results	Brain activity results
Koçak et al. 2011	OCD	12	27.0 ± 5.8	50 | 50	DSM-IV	20.2 ± 6.2	66% medicated	-	fMRI	Maintenance, suppression, or manipulation of a mental image.	↑performance score during suppression.	↓activity in R inferior parietal lobe, R posterior cingulate, and R superior frontal gyrus for all conditions.
	Healthy	12	25.1 ± 3.32	50 | 50		-	-					
Simon et al. 2014	OCD	21	33.1 ± 10.8	62 | 38	DSM-IV	21.2 ± 6.8	Medication-free; 33% CBT	-	fMRI	Appraisal or distraction of OCD-related, aversive, or neutral pictures.	-	↓activity in L amygdala, L dorsal anterior cingulate cortex, L insula, L postcentral gyrus, and R anterior cerebellum during distraction for OCD-related pictures.
	Healthy	21	33.1 ± 10.1	62 | 38		-	-					
Paul et al. 2016	OCD	24	31.7 ± 9.1	54 | 46	DSM-IV	22.2 ± 4.1	37% medicated; 37% CBT	↓ERQ reappraisal; ↓CERQ positive refocusing; ↑CERQ catastrophizing.	EEG	Cognitive reappraisal or cognitive distraction of neutral, aversive, and OCD-related pictures.	↓arousal for aversive pictures after reappraisal compared to distraction.	Unchanged Late Positive Potential amplitude during reappraisal and distraction (↓ healthy).
	Healthy	24	31.2 ± 8.2	54 | 46		-	-					
de Wit et al. 2015; Thorsen et al. 2019	OCD	43	37.6 ± 10.0	51 | 49	DSM-IV	21.6 ± 6.1	Unmedicated for ≥ 4 weeks	↓ERQ reappraisal.	fMRI	Cognitive reappraisal of fearful and OCD-related pictures.	↑distress reduction during OCD-related reappraisal.	Fear reappraisal: ↓ activity in R superior temporal gyrus and L middle frontal gyrus, and ↓ functional connectivity in L posterior insula and R amygdala; OCD-related reappraisal: ↑activity in R superior frontal gyrus ad R lingual gyrus (uncorrected results).
	Healthy	38	39.0 ± 11.3	53 | 47		0.0 ± 0.0	-					

Table 2 continues in the next page

Table 2 Summary of the studies with behavioral and/or neurobiological measures of cognitive regulation. The psychometrics and results comprise direct statistical comparisons between groups (OCD vs. healthy).

Study	Groups	Size	Age (years)	Gender (%F | %M)	Diagnosis	Y-BOCS	Treatment	Psychometrics	Technique	Task	Behavioral results	Brain activity results
Maria Picó-Pérez et al. 2019	OCD	73	37.7 ± 10.2	41 | 59	DSM-IV	22.1 ± 6.3	92% medicated	↓ERQ reappraisal and ↑ERQ suppression.	fMRI	-	-	Negative correlation between L amygdala - L posterior insula functional connectivity and reappraisal score in controls but not OCD.
	Healthy	42	39.4 ± 9.8	48 | 52		-	-					

OCD – obsessive-compulsive disorder; F – female; M – male; Y-BOCS – Yale-Brown Obsessive Compulsive Scale; DSM - Diagnostic and Statistical Manual of Mental Disorders; CBT – cognitive behavioral therapy; ERQ – Emotion Regulation Questionnaire; CERQ – Cognitive Emotion Regulation Questionnaire; fMRI – functional magnetic resonance imaging; EEG – electroencephalography; L – left; R – right.

The selected studies comprised mostly the cognitive regulation of thoughts, mental images, or pictures. The authors evaluated distress, disgust, arousal, and frequency of thoughts as the main behavioral outcomes, and brain activity/functional connectivity as neurobiological parameters. The tasks required the use of the following cognitive regulation strategies: suppression, distraction, acceptance, rescripting, and reappraisal.

The studies found that the suppression of negative/intrusive thoughts leads to an increase in the frequency of these thoughts during and after suppression (Janeck & Calamari, 1999; Najmi et al., 2009), and an augmentation of the distress elicited by the thoughts after suppression (Najmi et al., 2009) in OCD participants. Other authors found that the suppression of neutral thoughts (e.g. thinking about a "white bear") results in increased frequency of the target thought for OCD individuals solely during suppression (Tolin, Abramowitz, Hamlin, et al., 2002; Tolin, Abramowitz, Przeworski, et al., 2002). Moreover, Koçak and colleagues reported better performance for the OCD group during the suppression of an abstract mental image (Koçak et al., 2011). Najmi et al. (2009) demonstrated that the distress associated with intrusive thoughts was higher after using suppression when compared to distraction and acceptance strategies. Additionally, they demonstrated that intrusive thoughts were more frequent after the suppression in comparison to the acceptance condition in OCD patients. Lastly, they reported that the distress caused by intrusive thoughts diminished after applying acceptance strategies in OCD individuals (Najmi et al., 2009). Other authors reported a reduction of arousal for aversive pictures after using reappraisal compared to distraction techniques in OCD individuals (Paul et al., 2016), and a decrease of distress for OCD-related pictures during the reappraisal condition (De Wit et al., 2015; A. L. L. Thorsen et al., 2019). Fink and colleagues (Fink et al., 2018) also found decreased disgust ratings for OCD-related pictures after cognitive reappraisal in OCD and control participants, but no statistically significant differences between groups.

Cognitive reappraisal of fear-related pictures corresponded to decreased activity in the left middle frontal gyrus and right superior temporal gyrus, while reappraisal of OCD-related pictures increased activity in the right superior frontal gyrus and right lingual gyrus for OCD patients (De Wit et al., 2015; A. L. L. Thorsen et al., 2019). Moreover, these authors reported decreased functional connectivity in the left posterior insula and right amygdala during the reappraisal of fear-related images (De Wit et al., 2015; A. L. L. Thorsen et al., 2019). These results were in line with the altered correlation between functional connectivity of the left amygdala-left posterior insula and the reappraisal abilities in OCD individuals reported by other authors (Maria Picó-Pérez et al., 2019). Distraction strategies during the presentation of OCD-related pictures lead to decreased activity in a left cluster including the amygdala, dorsal ACC,

insula, and postcentral gyrus, and the right anterior cerebellum in OCD participants (Simon et al., 2014). Both reappraisal and distraction strategies during the visualization of pictures were associated with decreased responses in centro-parietal regions (late positive potential) in healthy participants but not in OCD patients (Paul et al., 2016). Lastly, suppression and manipulation of a mental image were linked to decreased activity in the right hemisphere in the inferior parietal lobule, posterior cingulate cortex, and superior frontal gyrus in OCD (Koçak et al., 2011). **Figure 2** contains a summary of these findings.

5. Discussion

Herein we systematically reviewed studies assessing cognitive regulation alterations in OCD in terms of behavioral, physiological, and neurobiological findings. Our results point to an advantageous effect of using cognitive reappraisal and acceptance strategies compared to suppression techniques to reduce distress and intrusive thoughts in OCD patients. Moreover, distraction seems to be more effective than suppression but less reliable when compared to reappraisal. Additionally, we observed altered brain responses in dlPFC/dorsomedial PFC (dmPFC), temporal, occipitotemporal, and centro-parietal regions during reappraisal in OCD participants. Reappraisal was also associated with functional connectivity changes between the amygdala and posterior insula in OCD. Distraction corresponded to decreased activity in limbic (amygdala, insula, and dorsal ACC), postcentral, and cerebellar regions in OCD. Lastly, suppression strategies were linked to decreased brain responses in dlPFC/dmPFC, posterior cingulate, and inferior parietal areas in OCD individuals.

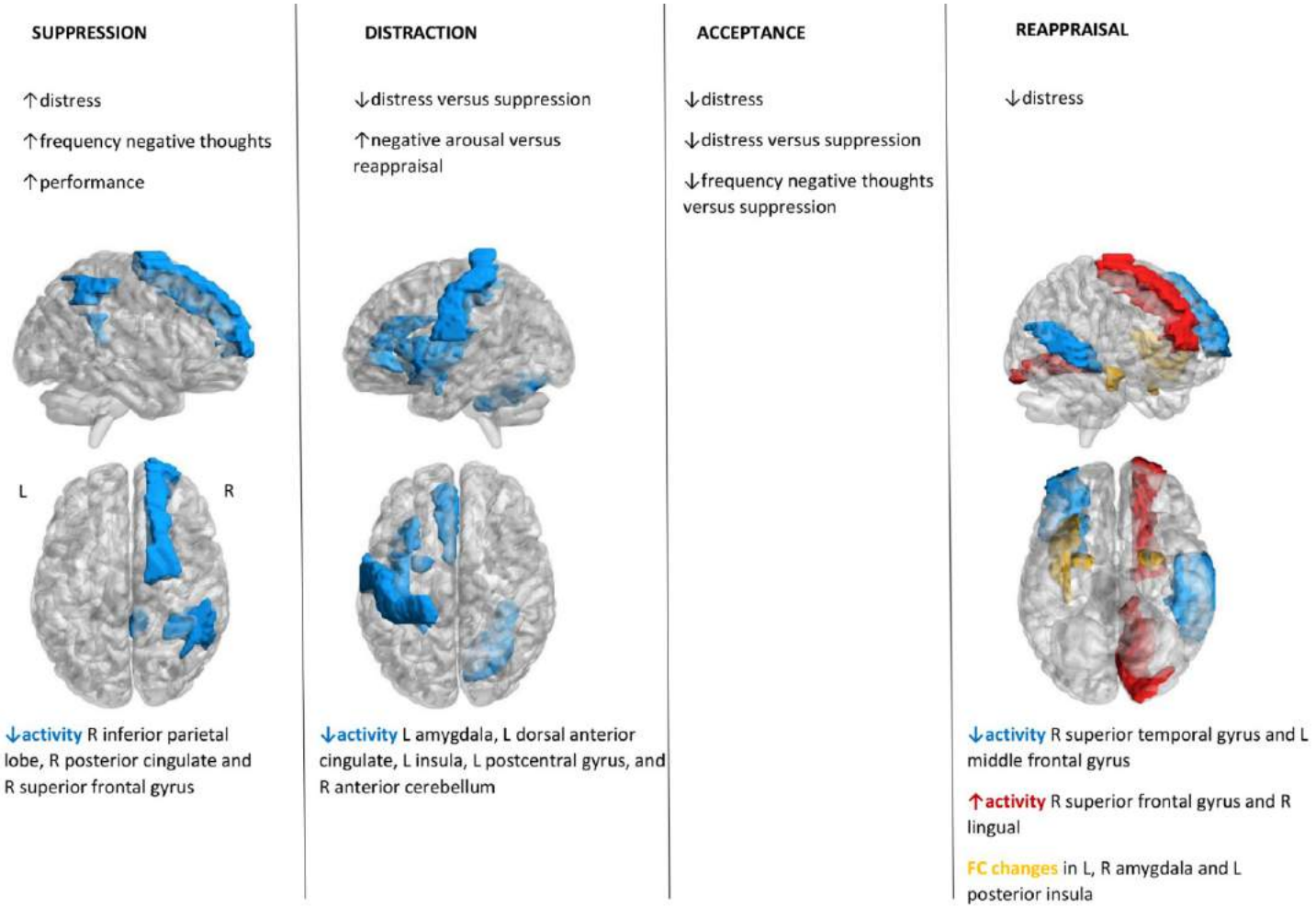


Figure 2 Summary of the systematic review of behavioral and neurobiological findings for the obsessive-compulsive versus the healthy control groups. R – right; L – left. The brain maps were created with the BrainNet Viewer (https://www.nitrc.org/projects/bnv/) using the Automated Anatomical Labelling atlas.

Psychiatric diseases are generally characterized by impaired emotion regulation abilities, with excessive suppression and reduced acceptance of emotions (Maria Picó-Pérez et al., 2017; Zilverstand et al., 2017). Previous literature using psychometric instruments demonstrated that OCD patients have difficulties in cognitive regulation. They reported increased deficits in emotion regulation, namely diminished reappraisal abilities and increased use of suppression strategies (Fernández de la Cruz et al., 2013; Yazici & Yazici, 2019). Some of the studies included in this review also indicated the same trend by using self-reported questionnaires (De Wit et al., 2015; Fink et al., 2018; Paul et al., 2016; Maria Picó-Pérez et al., 2019; A. L. L. Thorsen et al., 2019). The beneficial effect of reappraisal over suppression in OCD patients and other individuals has been supported by past findings (Dörfel et al., 2014; Goldberg et al., 2016; Webb et al., 2012). These authors denoted that reappraisal occurs before the complete unfolding of the emotional response and is more effective to control the negative impact of emotions, while the suppression process starts during the emotional response itself (Dörfel et al., 2014; Goldberg et al., 2016; Naragon-Gainey et al., 2017; Maria Picó-Pérez et al., 2018; Webb et al., 2012).

Suppression consists of the inhibition of emotions, physiological responses, or behaviors in face of stimuli (Dörfel et al., 2014; Goldberg et al., 2016; Maria Picó-Pérez et al., 2018). Thought suppression might become chronic if associated with unpleasant emotions and lead to increased frequency of suppressed thoughts (Najmi et al., 2009; Naragon-Gainey et al., 2017). Our findings support that suppression is a maladaptive strategy in OCD because it is linked to a subsequent higher occurrence of intrusive thoughts and enhanced distress (Janeck & Calamari, 1999; Najmi et al., 2009). Our results also showed that suppression is linked to increased internal attributions of weakness and incapacity to control intrusive thoughts in OCD (Tolin, Abramowitz, Hamlin, et al., 2002). Thus, OCD patients might often adopt suppression strategies as an effort to control obsessions (Najmi et al., 2009). Indeed, one of the studies included in this review showed that OCD patients have a higher performance during suppression (Koçak et al., 2011). In contrast to previous findings demonstrating increased responses in the dlPFC and inferior parietal cortex during suppression in healthy individuals (Dörfel et al., 2014), Koçak et al. (2011) found blunted superior frontal gyrus and inferior parietal lobule activity in OCD during suppression. The inferior parietal cortex is involved in shifting attention away from the self (Dörfel et al., 2014). The dlPFC involvement in cognitive regulation is discussed below. These altered responses in prefrontal and parietal cortices might underline the maladaptive use of suppression in OCD.

Distraction consists of shifting attention away from intrusive thoughts to focus on neutral/alternative stimulus (Dörfel et al., 2014; Moodie et al., 2020; Najmi et al., 2009; Webb et al., 2012). In this review, we observed that distraction reduces the distress elicited by intrusive thoughts when compared to

suppression (Najmi et al., 2009). Moreover, other authors indicated decreased responses in the amygdala, dorsal ACC, insula, postcentral gyrus, and cerebellum in OCD participants during distraction (Simon et al., 2014). Previous studies demonstrated increased responses in the ACC and parietal cortex and diminished activity in the amygdala and insula using distraction paradigms in healthy individuals (Dörfel et al., 2014; Moodie et al., 2020). The dorsal ACC and the inferior/superior parietal cortex are responsible for the allocation of attentional resources (Dörfel et al., 2014; Zilverstand et al., 2017) and present decreased activity during reappraisal in individuals with anxiety disorders (Zilverstand et al., 2017). The dorsal ACC is also associated with the update of working memory and performance monitoring (Dörfel et al., 2014), and provides the connection between areas involved in the appraisal of affective stimuli (e.g. amygdala) and vlPFC and dlPFC regions associated with the initiation and execution of regulation (Kohn et al., 2014). Thus, despite the indication of reduced distress and amygdala and insular activity with the use of distraction strategies, OCD patients might have functional impairment in ACC and parietal areas. Lastly, distraction seems to be effective in short-term to decrease stress and negative arousal but not as recurrent emotional regulation strategy, mainly when compared to reappraisal strategies (Dörfel et al., 2014; Naragon-Gainey et al., 2017; Webb et al., 2012), as reported by Paul and colleagues (Paul et al., 2016).

Acceptance refers to the experience of distressing situations without trying to alter their meaning (Najmi et al., 2009; Schäfer et al., 2017). Mindfulness techniques are based on acceptance, consisting of nonjudgmental awareness of an experience (Duckworth et al., 2018; Webb et al., 2012). Acceptance and mindfulness skills are stronger in individuals with distress tolerance (Naragon-Gainey et al., 2017). Moreover, the recurrent employment of acceptance is associated with reduced use of suppression and better outcomes for depression and anxiety disorders (Schäfer et al., 2017; Webb et al., 2012). Additionally, the acceptance and commitment therapy has beneficial effects for OCD patients namely in reducing the severity of obsessions, compulsions, anxiety, and depression (Bluett et al., 2014; Twohig et al., 2018). Thus, acceptance-based strategies might be adopted to treat OCD patients when standard cognitive-behavioral therapy (CBT) is unavailable.

Cognitive reappraisal involves the modification of the significance of initial appraisals (Buhle et al., 2014; Dörfel et al., 2014; Kohn et al., 2014; M. Picó-Pérez et al., 2019; Maria Picó-Pérez et al., 2018; Zilverstand et al., 2017). The most common reappraisal strategies are the reinterpretation of the stimuli with a more positive meaning or distancing from it with a viewing perspective of an unrelated observer (Dörfel et al., 2014; Duckworth et al., 2018; Goldberg et al., 2016; Moodie et al., 2020; M. Picó-Pérez et al., 2019; Maria Picó-Pérez et al., 2017; Webb et al., 2012; Zilverstand et al., 2017). In line with our

conclusions, the previous literature points to increased activity in the inferior frontal gyrus, posterior insula, and occipitotemporal regions, and decreased response in the dmPFC/dlPFC and temporal gyrus during cognitive reappraisal in patients with mood and anxiety disorders (Maria Picó-Pérez et al., 2017; Zilverstand et al., 2017). Moreover, studies with healthy individuals also reported the involvement of the dlPFC/dmPFC, parietal and temporal cortex, and the amygdala and insula in cognitive reappraisal processes (Buhle et al., 2014; Dörfel et al., 2014; Moodie et al., 2020; M. Picó-Pérez et al., 2019). The prefrontal alterations might indicate the deficient allocation of attention and impaired monitoring/manipulation of emotion-related information (Buhle et al., 2014; Dörfel et al., 2014; M. Picó-Pérez et al., 2019; Maria Picó-Pérez et al., 2017; Zilverstand et al., 2017). The increased activation of occipitotemporal regions might translate into enhanced attention to negative stimuli (Buhle et al., 2014; Maria Picó-Pérez et al., 2017). Additionally, the PFC and parietal cortex have a modulatory effect on lateral temporal regions associated with semantic and perceptual representations to alter the emotional significance of external stimuli (Buhle et al., 2014; Dörfel et al., 2014). In line with the findings of Paul et al. (2016) reviewed here, the downregulation of emotions during reappraisal is also linked to decreased late positive potential amplitude in centro-parietal regions, representing a reduction of sustained attention towards the negative stimuli (Zilverstand et al., 2017). Moreover, patients with anxiety disorders have decreased inferior/superior parietal responses during reappraisal of negative stimuli (Zilverstand et al., 2017) that might be associated with impaired inhibitory control (Maria Picó-Pérez et al., 2017) or blunted recruitment of attentional resources (Zilverstand et al., 2017). Thus, OCD patients seem to have impaired cognitive reappraisal processes because they did not present diminished late positive potential. Previous studies also found that healthy participants with higher reappraisal abilities have lower values of functional connectivity between the amygdala and anterior insula (Maria Picó-Pérez et al., 2018) and that the anterior insula activity is associated with the amygdala function during emotion regulation (Kohn et al., 2014). Additionally, the posterior insula and amygdala responses are down-regulated by reappraisal strategies (Dörfel et al., 2014). These authors suggest that the insula is involved in the selection of appropriate strategies to subsequently down-regulate the amygdala activity in the face of negative emotions. The absence of this association in OCD individuals (Maria Picó-Pérez et al., 2019) might indicate that their cognitive reappraisal deficits are underlined by the impaired functional connection between amygdalar and insular regions. The results from other authors included in our review also support impairments in functional connectivity in the amygdala and insula during fear reappraisal (De Wit et al., 2015; A. L. L. Thorsen et al., 2019).

CBT is one of the first-line treatments for OCD (O'Neill & Feusner, 2015; Stein et al., 2019) and aims at improving negative appraisals and dysfunctional beliefs with reappraisal strategies (Brooks & Stein, 2015; Buhle et al., 2014; Naragon-Gainey et al., 2017; Polman et al., 2009). After CBT, the activity in brain regions associated with affective processing (orbitofrontal cortex, ACC, thalamus and caudate) usually decreases and there is an enhancement of brain response in regions linked to neurocognitive processes (dlPFC, parietal cortex, putamen, and cerebellum) (Brooks & Stein, 2015; A. L. Thorsen et al., 2015). However, some studies also report the reduction of dlPFC activity after CBT (Brooks & Stein, 2015). Thus, CBT seems to restore prefrontal control over subcortical regions (Brooks & Stein, 2015) by increasing activity in frontal and parietal regions. Indeed, improved set-shifting, inhibitory, visuospatial, verbal memory, and working memory abilities have been reported after CBT and cognitive training (Vandborg et al., 2012). Moreover, dysfunctional beliefs decrease after CBT and cognitive therapy (Polman et al., 2009, 2011; Wolters et al., 2019), although other authors found controversial results (McLean et al., 2001; Olatunji et al., 2013).

Our conclusions are limited by the modest sample sizes (more than half of the studies with less than 30 participants per group), the concurrent medication and/or CBT (only three studies included patients without medication (De Wit et al., 2015; Simon et al., 2014; A. L. L. Thorsen et al., 2019)), and the inclusion of patients with comorbidities (e.g. major depressive disorder, anxiety disorders, and phobias; only one study reported the exclusion of comorbidities (Koçak et al., 2011)). Additionally, many of the studies did not provide information about the different OCD dimensions of the patients included, hindering the comparison between patients with different symptomatology. Moreover, the majority of the studies explored suppression and reappraisal strategies, preventing the extraction of robust information for other strategies (e.g. acceptance). Most of the studies employed emotion-related stimuli or paradigms analyzing intrusive thoughts (except (Koçak et al., 2011)). OCD is also characterized by an imbalance between cognitive and reward pathways that explains the execution of rewarding compulsive actions in response to uncontrollable obsessional thoughts (Xie et al., 2017). Thus, tasks of cognitive regulation of reward processing are critical for future studies (Brandl et al., 2019). Lastly, some studies might have not been included in this review because our search process was conducted only in the Medline database. However, we complemented our search with reference lists.

To better tackle the cognitive regulation alterations in OCD, future studies should use cognitive regulation tasks assessing behavioral parameters (e.g. distress, anxiety and occurrence of intrusive thoughts) in combination with neuroimaging methods with the additional incorporation of physiological measures (e.g. heart and respiratory rate and skin conductance) to obtain objective parameters of

anxiety/distress changes. Moreover, the inclusion of treatment naïve patients and the use of larger samples is crucial. Additionally, the use of more ecological/personalized approaches might be more appropriate to disentangle the mechanisms involved (e.g. asking OCD participants to regulate their obsessions without using other external stimuli) (Webb et al., 2012).

This review provides further insight into the cognitive regulation alterations in OCD that might guide the improvement of cognitive therapy and CBT. Overall, we observed altered brain responses in regions belonging to the frontoparietal network (dlPFC/dmPFC, inferior/superior parietal cortex, and superior temporal cortex) during cognitive regulation. This conclusion suggests an impairment in attention allocation and deficient control of emotion-related information (Cocchi et al., 2013; Nigg, 2017). Moreover, this review corroborates the superior effect of reappraisal and acceptance strategies and the detrimental effect of suppression approaches regarding the reduction of distress and frequency of intrusive thoughts after cognitive regulation.

6. Funding

This work has been funded by National funds, through the Foundation for Science and Technology (FCT) - project UIDB/50026/2020 and UIDP/50026/2020; and by the projects NORTE-01-0145-FEDER-000013 and NORTE-01-0145-FEDER-000023, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). SF was supported by a combined Ph.D. scholarship from the FCT and the company iCognitus4ALL – IT Solutions, Lda (grant number PD/BDE/127839/2016).

7. References

Ahern, C., Kyrios, M., & Meyer, D. (2015). Exposure to unwanted intrusions, neutralizing and their effects on self-worth and obsessive-compulsive phenomena. Journal of Behavior Therapy and Experimental Psychiatry, 49, 216–222. https://doi.org/10.1016/j.jbtep.2015.07.008

American Psychiatric Association. (2013). Diagnostic Statistical Manual of Mental Disorders (DSM-5). In American Psychiatric Association (5th, revised ed.). American Psychiatric Association Pub, 2013.

Bluett, E. J., Homan, K. J., Morrison, K. L., Levin, M. E., & Twohig, M. P. (2014). Acceptance and commitment therapy for anxiety and OCD spectrum disorders: An empirical review. Journal of Anxiety Disorders, 28(6), 612–624. https://doi.org/10.1016/j.janxdis.2014.06.008

Brandl, F., Le Houcq Corbi, Z., Mulej Bratec, S., & Sorg, C. (2019). Cognitive reward control recruits medial and lateral frontal cortices, which are also involved in cognitive emotion regulation: A coordinate-based meta-analysis of fMRI studies. NeuroImage, 200(August 2018), 659–673. https://doi.org/10.1016/j.neuroimage.2019.07.008

Brooks, S. J., & Stein, D. J. (2015). A systematic review of the neural bases of psychotherapy for anxiety and related disorders. Dialogues in Clinical Neuroscience, 17(3), 261–279. http://www.ncbi.nlm.nih.gov/pubmed/26487807

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., & Ochsner, K. N. (2014). Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. Cerebral Cortex, 24(11), 2981–2990. https://doi.org/10.1093/cercor/bht154

Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. Trends in Cognitive Sciences, 17(10), 493–501. https://doi.org/10.1016/j.tics.2013.08.006

De Wit, S. J., Van Der Werf, Y. D., Mataix-Cols, D., Trujillo, J. P., Van Oppen, P., Veltman, D. J., & van den Heuvel, O. A. (2015). Emotion regulation before and after transcranial magnetic stimulation in obsessive compulsive disorder. Psychological Medicine, 45(14), 3059–3073. https://doi.org/10.1017/S0033291715001026

Dörfel, D., Lamke, J.-P., Hummel, F., Wagner, U., Erk, S., & Walter, H. (2014). Common and differential neural networks of emotion regulation by Detachment, Reinterpretation, Distraction, and Expressive Suppression: A comparative fMRI investigation. NeuroImage, 101, 298–309. https://doi.org/10.1016/j.neuroimage.2014.06.051

Duckworth, A. L., Milkman, K. L., & Laibson, D. (2018). Beyond Willpower: Strategies for Reducing Failures of Self-Control. Psychological Science in the Public Interest, 19(3), 102–129. https://doi.org/10.1177/1529100618821893

Fernández de la Cruz, L., Landau, D., Iervolino, A. C., Santo, S., Pertusa, A., Singh, S., & Mataix-Cols, D. (2013). Experiential avoidance and emotion regulation difficulties in hoarding disorder. Journal of Anxiety Disorders, 27(2), 204–209. https://doi.org/10.1016/j.janxdis.2013.01.004

Fink, J., Pflugradt, E., Stierle, C., & Exner, C. (2018). Changing disgust through imagery rescripting and cognitive reappraisal in contamination-based obsessive-compulsive disorder. Journal of Anxiety Disorders, 54(January), 36–48. https://doi.org/10.1016/j.janxdis.2018.01.002

García-Soriano, G., & Belloch, A. (2013). Symptom dimensions in obsessive-compulsive disorder: Differences in distress, interference, appraisals and neutralizing strategies. Journal of Behavior Therapy and Experimental Psychiatry, 44(4), 441–448. https://doi.org/10.1016/j.jbtep.2013.05.005

Goldberg, X., Cardoner, N., Alonso, P., López-Solà, C., Real, E., Hernández-Ribas, R., Jiménez-Murcia, S., Subirà, M., Segalàs, C., Menchón, J. M., & Soriano-Mas, C. (2016). Inter-individual variability in emotion regulation: Pathways to obsessive-compulsive symptoms. Journal of Obsessive-Compulsive and Related Disorders, 11, 105–112. https://doi.org/10.1016/j.jocrd.2016.10.002

Gruner, P., & Pittenger, C. (2017). Cognitive inflexibility in Obsessive-Compulsive Disorder. Neuroscience, 345(August), 243–255. https://doi.org/10.1016/j.neuroscience.2016.07.030

Hallion, L. S., Tolin, D. F., Billingsley, A. L., Kusmierski, S. N., & Diefenbach, G. J. (2019). "Cold" Cognitive Control and Attentional Symptoms in Anxiety: Perceptions Versus Performance. Behavior Therapy, 50(6), 1150–1163. https://doi.org/10.1016/j.beth.2019.04.002

Hezel, D. M., & McNally, R. J. (2016). A Theoretical review of cognitive biases and deficits in obsessive–compulsive disorder. Biological Psychology, 121, 221–232. https://doi.org/10.1016/j.biopsycho.2015.10.012

Janeck, A. S., & Calamari, J. E. (1999). Thought suppression in obsessive-compulsive disorder. Cognitive Therapy and Research, 23(5), 497–509. https://doi.org/10.1023/A:1018720404750

Kikul, J., Vetter, J., Lincoln, T. M., & Exner, C. (2011). Effects of cognitive self-consciousness on visual memory in obsessive-compulsive disorder. Journal of Anxiety Disorders, 25(4), 490–497. https://doi.org/10.1016/j.janxdis.2010.12.002

Koçak, O. M., Özpolat, A. Y., Atbaşoğlu, C., & Çiçek, M. (2011). Cognitive control of a simple mental image in patients with obsessive–compulsive disorder. Brain and Cognition, 76(3), 390–399. https://doi.org/10.1016/j.bandc.2011.03.020

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). NeuroImage Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. NeuroImage, 87, 345–355. https://doi.org/10.1016/j.neuroimage.2013.11.001

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Medicine, 6(7), e1000100. https://doi.org/10.1371/journal.pmed.1000100

McLean, P. D., Whittal, M. L., Thordarson, D. S., Taylor, S., Söchting, I., Koch, W. J., Paterson, R., & Anderson, K. W. (2001). Cognitive versus behavior therapy in the group treatment of Obsessive-Compulsive disorder. Journal of Consulting and Clinical Psychology, 69(2), 205–214. https://doi.org/10.1037/0022-006X.69.2.205

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine, 6(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Moodie, C. A., Suri, G., Goerlitz, D. S., Mateen, M. A., Sheppes, G., McRae, K., Lakhan-Pal, S., Thiruchselvam, R., & Gross, J. J. (2020). The neural bases of cognitive emotion regulation: The roles of strategy and intensity. Cognitive, Affective, & Behavioral Neuroscience, 20(2), 387–407. https://doi.org/10.3758/s13415-020-00775-8

Morillo, C., Belloch, A., & García-Soriano, G. (2007). Clinical obsessions in obsessive–compulsive patients and obsession-relevant intrusive thoughts in non-clinical, depressed and anxious subjects: Where are the differences? Behaviour Research and Therapy, 45(6), 1319–1333. https://doi.org/10.1016/j.brat.2006.11.005

Najmi, S., Reese, H., Wilhelm, S., Fama, J., Beck, C., & Wegner, D. M. (2010). Learning the Futility of the Thought Suppression Enterprise in Normal Experience and in Obsessive Compulsive Disorder. Behavioural and Cognitive Psychotherapy, 38(1), 1–14. https://doi.org/10.1017/S1352465809990439

Najmi, S., Riemann, B. C., & Wegner, D. M. (2009). Managing unwanted intrusive thoughts in obsessive-compulsive disorder: Relative effectiveness of suppression, focused distraction, and acceptance. Behaviour Research and Therapy, 47(6), 494–503. https://doi.org/10.1016/j.brat.2009.02.015

Naragon-Gainey, K., McMahon, T. P., & Chacko, T. P. (2017). The structure of common emotion regulation strategies: A meta-analytic examination. Psychological Bulletin, 143(4), 384–427. https://doi.org/10.1037/bul0000093

Nigg, J. T. (2017). Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. Journal of Child Psychology and Psychiatry, 58(4), 361–383. https://doi.org/10.1111/jcpp.12675

O'Neill, J., & Feusner, J. (2015). Cognitive-behavioral therapy for obsessive– compulsive disorder: access to treatment, prediction of long-term outcome with neuroimaging. Psychology Research and Behavior Management, 8, 211. https://doi.org/10.2147/PRBM.S75106

Olatunji, B. O., Rosenfield, D., Tart, C. D., Cottraux, J., Powers, M. B., & Smits, J. A. J. (2013). Behavioral versus cognitive treatment of obsessive-compulsive disorder: An examination of outcome and mediators of change. Journal of Consulting and Clinical Psychology, 81(3), 415–428. https://doi.org/10.1037/a0031865

Paul, S., Simon, D., Endrass, T., & Kathmann, N. (2016). Altered emotion regulation in obsessive-compulsive disorder as evidenced by the late positive potential. Psychological Medicine, 46(1), 137–147. https://doi.org/10.1017/S0033291715001610

Picó-Pérez, M., Alemany-Navarro, M., Dunsmoor, J. E., Radua, J., Albajes-Eizagirre, A., Vervliet, B., Cardoner, N., Benet, O., Harrison, B. J., Soriano-Mas, C., & Fullana, M. A. (2019). Common and distinct neural correlates of fear extinction and cognitive reappraisal: A meta-analysis of fMRI studies. Neuroscience & Biobehavioral Reviews, 104(June), 102–115. https://doi.org/10.1016/j.neubiorev.2019.06.029

Picó-Pérez, Maria, Alonso, P., Contreras-Rodríguez, O., Martínez-Zalacaín, I., López-Solà, C., Jiménez-Murcia, S., Verdejo-García, A., Menchón, J. M., & Soriano-Mas, C. (2018). Dispositional use of emotion regulation strategies and resting-state cortico-limbic functional connectivity. Brain Imaging and Behavior, 12(4), 1022–1031. https://doi.org/10.1007/s11682-017-9762-3

Picó-Pérez, Maria, Ipser, J., Taylor, P., Alonso, P., López-Solà, C., Real, E., Segalàs, C., Roos, A., Menchón, J. M., Stein, D. J., & Soriano-Mas, C. (2019). Intrinsic functional and structural connectivity of emotion regulation networks in obsessive-compulsive disorder. Depression and Anxiety, 36(2), 110–120. https://doi.org/10.1002/da.22845

Picó-Pérez, Maria, Moreira, P. S., Ferreira, V. D. M., Radua, J., Mataix-Cols, D., Sousa, N., Soriano-Mas, C., & Morgado, P. (2020). Modality-specific overlaps in brain structure and function in Obsessive-compulsive disorder: multimodal meta-analysis of case-control MRI studies. Neuroscience & Biobehavioral Reviews. https://doi.org/10.1016/j.neubiorev.2020.01.033

Picó-Pérez, Maria, Radua, J., Steward, T., Menchón, J. M., & Soriano-Mas, C. (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 79(January), 96–104. https://doi.org/10.1016/j.pnpbp.2017.06.001

Polman, A., Bouman, T. K., van Geert, P. L. C., de Jong, P. J., & den Boer, J. A. (2011). Dysfunctional beliefs in the process of change of cognitive treatment in obsessive compulsive checkers. Clinical Psychology & Psychotherapy, 18(3), 256–273. https://doi.org/10.1002/cpp.707

Polman, A., Bouman, T. K., van Hout, W. J. P. J., de Jong, P. J., & den Boer, J. A. (2009). Processes of change in cognitive-behavioural treatment of obsessive-compulsive disorder: Current status and some future directions. Clinical Psychology & Psychotherapy, 17(1), n/a-n/a. https://doi.org/10.1002/cpp.638

Purdon, C., Rowa, K., & Antony, M. M. (2005). Thought suppression and its effects on thought frequency, appraisal and mood state in individuals with obsessive-compulsive disorder. Behaviour Research and Therapy, 43(1), 93–108. https://doi.org/10.1016/j.brat.2003.11.007

Rasgon, A., Lee, W. H., Leibu, E., Laird, A., Glahn, D., Goodman, W., & Frangou, S. (2017). Neural correlates of affective and non-affective cognition in obsessive compulsive disorder: A meta-analysis of functional imaging studies. European Psychiatry, 46, 25–32. https://doi.org/10.1016/j.eurpsy.2017.08.001

Salkovskis, P. M., Thorpe, S. J., Wahl, K., Wroe, A. L., & Forrester, E. (2003). Neutralizing increases discomfort associated with obsessional thoughts: An experimental study with obsessional patients. Journal of Abnormal Psychology, 112(4), 709–715. https://doi.org/10.1037/0021-843X.112.4.709

Schäfer, J. Ö., Naumann, E., Holmes, E. A., Tuschen-Caffier, B., & Samson, A. C. (2017). Emotion Regulation Strategies in Depressive and Anxiety Symptoms in Youth: A Meta-Analytic Review. Journal of Youth and Adolescence, 46(2), 261–276. https://doi.org/10.1007/s10964-016-0585-0

Simon, D., Adler, N., Kaufmann, C., & Kathmann, N. (2014). Amygdala hyperactivation during symptom provocation in obsessive-compulsive disorder and its modulation by distraction. NeuroImage: Clinical, 4, 549–557. https://doi.org/10.1016/j.nicl.2014.03.011

Stein, D. J., Costa, D. L. C., Lochner, C., Miguel, E. C., Reddy, Y. C. J., Shavitt, R. G., van den Heuvel, O. A., & Simpson, H. B. (2019). Obsessive–compulsive disorder. Nature Reviews Disease Primers, 5(1), 52. https://doi.org/10.1038/s41572-019-0102-3

Thorsen, A. L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., & van den Heuvel, O. A. (2018). Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-analysis of 25 Functional Neuroimaging Studies. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3(6), 563–571. https://doi.org/10.1016/J.BPSC.2018.01.009

Thorsen, A. L. L., de Wit, S. J. J., de Vries, F. E. E., Cath, D. C. C., Veltman, D. J. J., van der Werf, Y. D. D., Mataix-Cols, D., Hansen, B., Kvale, G., & van den Heuvel, O. A. A. (2019). Emotion Regulation in Obsessive-Compulsive Disorder, Unaffected Siblings, and Unrelated Healthy Control Participants. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4(4), 352–360. https://doi.org/10.1016/j.bpsc.2018.03.007

Thorsen, A. L., van den Heuvel, O. A., Hansen, B., & Kvale, G. (2015). Neuroimaging of psychotherapy for obsessive–compulsive disorder: A systematic review. Psychiatry Research: Neuroimaging, 233(3), 306–313. https://doi.org/10.1016/j.pscychresns.2015.05.004

Tolin, D. F., Abramowitz, J. S., Hamlin, C., Foa, E. B., & Synodi, D. S. (2002). Attributions for thought suppression failure in obsessive-compulsive disorder. Cognitive Therapy and Research, 26(4), 505–517. https://doi.org/10.1023/A:1016559117950

Tolin, D. F., Abramowitz, J. S., Przeworski, A., & Foa, E. B. (2002). Thought suppression in obsessive-compulsive disorder. Behaviour Research and Therapy, 40(11), 1255–1274. https://doi.org/10.1016/S0005-7967(01)00095-X

Twohig, M. P., Abramowitz, J. S., Smith, B. M., Fabricant, L. E., Jacoby, R. J., Morrison, K. L., Bluett, E. J., Reuman, L., Blakey, S. M., & Ledermann, T. (2018). Adding acceptance and commitment therapy to exposure and response prevention for obsessive-compulsive disorder: A randomized controlled trial. Behaviour Research and Therapy, 108(February), 1–9. https://doi.org/10.1016/j.brat.2018.06.005

Vandborg, S. K. J. Æ. R., Hartmann, T. U. E. B., Bennedsen, B. E., Pedersen, A. D., Eskildsen, A., Bror, P., & Videbech, H. (2012). Do cognitive functions in obsessive – compulsive disorder change after

treatment ? A systematic review and a double case report. 6. https://doi.org/10.3109/08039488.2011.626869

Webb, T. L., Miles, E., & Sheeran, P. (2012). Dealing with feeling: A meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. Psychological Bulletin, 138(4), 775–808. https://doi.org/10.1037/a0027600

Wolters, L. H., Garst, P. J. M. P. G. J. A., Boer, S. M. H. F., & Haan, L. V. E. De. (2019). Mediating Mechanisms in Cognitive Behavioral Therapy for Childhood OCD : The Role of Dysfunctional Beliefs. Child Psychiatry & Human Development, 50(2), 173–185. https://doi.org/10.1007/s10578-018-0830-8

Xie, C., Ma, L., Jiang, N., Huang, R., Li, L., Gong, L., He, C., Xiao, C., Liu, W., Xu, S., & Zhang, Z. (2017). Imbalanced functional link between reward circuits and the cognitive control system in patients with obsessive-compulsive disorder. Brain Imaging and Behavior, 11(4), 1099–1109. https://doi.org/10.1007/s11682-016-9585-7

Yazici, K. U., & Yazici, I. P. (2019). Decreased theory of mind skills, increased emotion dysregulation and insight levels in adolescents diagnosed with obsessive compulsive disorder. Nordic Journal of Psychiatry, 73(7), 462–469. https://doi.org/10.1080/08039488.2019.1652341

Zetsche, U., Rief, W., Westermann, S., & Exner, C. (2015). Cognitive deficits are a matter of emotional context: Inflexible strategy use mediates context-specific learning impairments in OCD. Cognition and Emotion, 29(2), 360–371. https://doi.org/10.1080/02699931.2014.911144

Zilverstand, A., Parvaz, M. A., & Goldstein, R. Z. (2017). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. NeuroImage, 151(8), 105–116. https://doi.org/10.1016/j.neuroimage.2016.06.009

CHAPTER II

Stress influences the effect of obsessive-compulsive symptoms on emotion regulation

Sónia Ferreira, Beatriz Couto, Mafalda Sousa, Rita Vieira, Nuno Sousa, Maria Picó-Pérez, Pedro Morgado

Manuscript submitted for publication

Stress influences the effect of obsessive-compulsive symptoms on emotion regulation

Sónia Ferreira[1,2,3], Beatriz Couto[1,2,3], Mafalda Sousa[1,2,3], Rita Vieira[1,2,3], Nuno Sousa[1,2,3], Maria Picó-Pérez[1,2,3], Pedro Morgado[1,2,3]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [2]ICVS-3Bs PT Government Associate Laboratory, Braga/Guimarães, Portugal; [3]Clinical Academic Center-Braga (2CA), Braga, Portugal

1. Abstract

Obsessive-compulsive disorder (OCD) is characterized by emotion regulation impairments, namely the frequent use of maladaptive strategies such as suppression and the decreased use of reappraisal strategies. Additionally, these patients exhibit elevated stress levels. Since stress exposure affects emotion regulation abilities, stress might influence the relationship between obsessive-compulsive symptoms and emotion regulation. In this study, we explored the effects of stress and obsessive-compulsive symptoms on emotion regulation in a sample of healthy and OCD individuals. We used self-reported psychometric scales to measure stress levels, obsessive-compulsive symptoms, and emotion reappraisal and suppression skills. We applied multiple regression and mediation analyses. Our results demonstrated that increased reappraisal scores were associated with higher suppression scores. Additionally, elevated stress values predicted increased scores for suppression and decreased scores for reappraisal. Furthermore, the reappraisal abilities resulted from a combination of direct effects of obsessive-compulsive symptoms and indirect effects of obsessive-compulsive symptoms mediated by stress. Thus, the reliance on suppression strategies and the difficulty in using reappraisal approaches are explained by stress levels and are not directly explained by obsessive-compulsive symptoms. This study highlights the necessity of targeting stress symptoms in current therapy-based treatments for OCD.

2. Introduction

Obsessive-compulsive disorder (OCD) may arise from an interplay between genetic and environmental risk factors, namely exposure to stressful and traumatic life events (Adams et al., 2018; Brander et al., 2016). Moreover, increases in general stress (e.g. job loss and family disease) and changes in routines throughout life are features associated with the development (Coles et al., 2011) and severity (Lin et al., 2007) of OCD. OCD is characterized by elevated levels of anxiety and distress elicited by the presence of intrusive thoughts (obsessions) (American Psychiatric Association, 2013). The enhanced levels of distress might increase the hypothalamic-pituitary-adrenal (HPA) axis function resulting in an augmented stress response (Sousa-Lima et al., 2019). In line with this assumption, previous studies have found a positive correlation between perceived stress levels and obsessive symptoms in OCD individuals (P. Morgado et al., 2013). Additionally, other researchers demonstrated that increased cortisol levels are a hallmark of OCD also suggesting the hyperactivity of the HPA axis (P. Morgado et al., 2013; Sousa-Lima et al., 2019). Furthermore, brain anatomical and functional alterations in the striatum (caudate and putamen), hippocampus, amygdala, and medial and orbitofrontal prefrontal cortices have been reported for OCD and stress, suggesting that stress may exacerbate the bias towards habitual and ritualistic compulsive behaviors in OCD patients (Adams et al., 2018; Pedro Morgado et al., 2015; Maria Picó-Pérez et al., 2020; N. Sousa, 2016; Nuno Sousa & Almeida, 2012).

OCD is also characterized by emotional regulation deficits (X. Goldberg et al., 2016; Maria Picó-Pérez et al., 2019; A. L. L. Thorsen et al., 2019; Zilverstand et al., 2017). Past research has shown that OCD patients frequently suppress their emotions instead of using more beneficial reappraisal strategies (De Wit et al., 2015; Fernández de la Cruz et al., 2013; Fink et al., 2018; Paul et al., 2016; Yazici & Yazici, 2019). The constant use of suppression has counterproductive effects leading to more distress and intrusive thoughts (Janeck & Calamari, 1999; Najmi et al., 2009).

The emotional appraisal and regulation processes are linked to stress mechanisms. Acute and social stressors lead to the engagement of maladaptive emotion regulation strategies such as worry and rumination (Denson et al., 2009). Thus, the chronic use of these strategies might in turn augment the stress response. Indeed, maladaptive emotion regulation strategies have been associated with increased stress responses (Denson et al., 2009; Lewis et al., 2018), while reappraisal led to enhanced stress recovery (Lewis et al., 2018) in healthy participants and individuals with anxiety disorders. A recent meta-analysis also reported that reappraisal of fear/negative emotions induced by stressful tasks decreases

the heart rate in healthy individuals (Zaehringer et al., 2020). Moreover, emotion regulation difficulties translate into decreased heart rate variability (Aldao & Mennin, 2012; Visted et al., 2017), a well-known biomarker of stress (Kim et al., 2018). Lastly, diminished cortisol and perceived stress levels in response to an acute stressor were observed after cognitive-behavioral stress management (Gaab et al., 2003). These authors reported that the alterations in stress response were associated with changes in emotion appraisal.

In this way, stress may play a significant role in the relationship between OCD and emotion regulation. In this study, we aim to investigate the impact of stress and obsessive-compulsive (OC) symptoms on emotion regulation in a sample of non-psychiatric and OCD individuals using psychometric instruments. Based on the previous literature, we assume that higher scores for stress and OC symptoms are associated with impairments in emotion reappraisal and the enhanced use of emotion suppression strategies. Furthermore, we hypothesize that stress mediates the effect of OC symptoms on emotion regulation. This study elucidates the role of stress on OCD providing new recommendations for current psychotherapy approaches.

3. Methods

a. Participants

We included OCD patients and non-psychiatric control participants in this study. The OCD patients were recruited at the Psychiatry Unit of *Hospital de Braga* (Braga, Portugal) and diagnosed by a psychiatrist (PM) with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The patients were under treatment as usual or were treatment naïve. We excluded patients with a history of neurological disorders. The control participants were recruited among the local community accordingly to the age, gender, and education of the patients, and did not had a history of psychiatric/neurological disorders.

All participants signed an informed consent. The study was approved by the ethics committees of *Hospital de Braga* (*Comissão de Ética para a Saúde*) and University of Minho (*Subcomissão de Ética para as Ciências da Vida e da Saúde*) and respected the Declaration of Helsinki principles.

b. Psychometric evaluation

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was applied to evaluate the disease severity in OCD patients (Castro-Rodrigues et al., 2018; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989). We also applied the Emotion Regulation Questionnaire (ERQ) to measure reappraisal and suppression abilities (Gross & John, 2003; Vaz et al., 2014). The Obsessive-Compulsive Inventory-Revised (OCI-R) was also used to measure OCD severity and dimensions (washing, checking, ordering, hoarding, obsessing, and neutralizing subscales) (Abramowitz & Deacon, 2006; Foa et al., 2002). The 10-items Perceived Stress Scale (PSS-10) was also applied to quantify self-perceived stress levels (S. Cohen et al., 1983; P. Morgado et al., 2013; Trigo et al., 2010).

c. Statistical analysis

The statistical analysis was performed with JASP (version 0.11.1; JASP Team, University of Amsterdam, The Netherlands). *P*-values under 0.05 were considered statistically significant. All statistical tests were two-tailed.

First, we evaluated differences in demographic (age, gender, and education) and psychometric (ERQ reappraisal and suppression, PSS-10, and OCI-R total and subscales) variables between the OCD and control group using independent samples *t*-tests (and the chi-squared test for gender [χ^2]). We used Bonferroni correction for multiple comparisons in the OCI-R subscales (washing, checking, ordering, hoarding, obsessing, and neutralizing).

Moreover, we explored the association among the variables (age, education, ERQ reappraisal and suppression, PSS-10, and OCI-R total) for all the sample and within each group (OCD and control) using Pearson's correlations. We used Bonferroni correction to correct for multiple comparisons.

After, we used two multiple regression models to study which demographic and psychometric variables predicted the ERQ reappraisal and ERQ suppression scores in the total sample. We tested the following predictors: age, gender, education, PSS-10, OCI-R total, and ERQ reappraisal/ERQ suppression.

Lastly, we performed a mediation analysis to understand if the OCI-R total score (predictor variable) predicted the ERQ reappraisal and suppression scores (outcome variables) when mediated by the PSS-10 score (mediator variable), using age, gender, and education as background confounders. We applied

the bias-corrected bootstrap method with 1000 replications (Biesanz et al., 2010). This analysis was performed using the total sample.

4. Results

We included 43 OCD patients and 22 control participants. One OCD patient was excluded because he/she did not fill the OCI-R scale. Three patients were treatment naïve, 3 patients were not under medication, and the other patients were taking psychotropic medication (clomipramine, fluoxetine, fluvoxamine, sertraline, or escitalopram). Nine patients were being treated with psychotherapy (13 patients with missing information).

Table 1 contains the descriptive and statistical values for the demographic and psychometric data. The OCD and control groups were not different in terms of age, gender ratio, and education level. Additionally, we observed statistically significant increases in the PSS-10 score, and the OCI-R total, washing, checking, obsessing, and neutralizing scores in the OCD group. Moreover, the OCD participants had decreased scores for the ERQ reappraisal subscale.

Table 2 summarizes the Pearson's correlations results for the complete sample. We observed a negative association between age and education, and a positive correlation between the OCI-R and PSS-10 scores. Within the OCD group, we found a positive correlation between the OCI-R and PSS-10 scores (Supplementary **Table S1**). For the control group, we did not detect statistically significant correlations after correcting for multiple comparisons (Supplementary **Table S2**). However, the significant correlations for the complete sample were also present in the OCD and control groups at uncorrected *p*-values (supplementary **Tables S1** and **S2**).

Table 1 Description of the demographic and psychometric variables for the obsessive-compulsive and control group and for the total sample, and representation of the statistical differences between groups (independent samples *t*-test and chi-squared test χ^2; p_{bonf} - *p*-value after Bonferroni correction; *d* – Cohen's effect size).

	OCD (n = 42)	Control (n = 22)	Total sample (n = 64)	Statistical results between groups (OCD versus control)
Age (years)	30. 9 ± 10.9	29.5 ± 12.6	30.4 ± 11.4	$t_{(62)} = 0.48$; $p = 0.633$; $d = 0.13$
Gender (F | M)	27 | 15	13 | 9	40 | 24	$\chi^2_{(1)} = 0.17$; $p = 0.683$
Education (years)	13.5 ± 3.9	13.1 ± 4.1	13.4 ± 4.0	$t_{(62)} = 0.41$; $p = 0.682$; $d = 0.11$
Y-BOCS†				
Total	28.1 ± 6.6	-	-	-
Obsessions	13.6 ± 4.1	-	-	-
Compulsions	14.5 ± 2.9	-	-	-
ERQ				
Reappraisal	24.9 ± 9.5	30.1 ± 7.9	26.7 ± 9.3	$t_{(62)} = -2.19$; $p = 0.032$; $d = -0.58$*
Suppression	14.3 ± 5.1	15.0 ± 5.9	14.5 ± 5.4	$t_{(62)} = -0.53$; $p = 0.595$; $d = -0.14$
PSS-10	22.3 ± 8.0	15.4 ± 7.2	19.9 ± 8.3	$t_{(62)} = 3.40$; $p = 0.001$; $d = 0.89$*
OCI-R				
Total	31.8 ± 14.0	15.4 ± 10.3	26.2 ± 15.0	$t_{(62)} = 4.82$; $p = 9.777\times10^{-6}$; $d = 1.27$*
Washing	5.3 ± 3.9	1.3 ± 2.0	3.9 ± 3.9	$t_{(62)} = 4.38$; $p_{bonf} = 2.770\times10^{-4}$; $d = 1.15$*
Checking	5.6 ± 3.7	2.2 ± 2.1	4.4 ± 3.6	$t_{(62)} = 4.00$; $p_{bonf} = 0.001$; $d = 1.05$*
Ordering	5.5 ± 3.5	3.9 ± 2.4	5.0 ± 3.3	$t_{(62)} = 1.89$; $p_{bonf} = 0.378$; $d = 0.50$
Hoarding	3.6 ± 3.2	3.5 ± 3.0	3.6 ± 3.1	$t_{(62)} = 0.09$; $p_{bonf} = 1.000$; $d = 0.02$
Obsessing	7.7 ± 3.5	2.8 ± 2.8	6.0 ± 4.0	$t_{(62)} = 5.60$; $p_{bonf} = 3.111\times10^{-6}$; $d = 1.47$*
Neutralizing	4.1 ± 3.7	1.6 ± 1.8	3.3 ± 3.4	$t_{(62)} = 2.97$; $p_{bonf} = 0.024$; $d = 0.78$*

Data represents mean ± standard deviation; OCD – obsessive-compulsive disorder; F – female; M – male; Y-BOCS – Yale-Brown Obsessive Compulsive Scale; ERQ – Emotion Regulation Questionnaire; PSS-10 – Perceived Stress Scale (10 items); OCI-R – Obsessive-Compulsive Inventory-Revised; †Four patients with missing data; *Statistically significant differences between groups.

Table 2 Results of Pearson's correlation among demographic and psychometric variables for the complete sample (p_{bonf} - p-value after Bonferroni correction).

	Education (years)	ERQ reappraisal	ERQ suppression	PSS-10	OCI-R total
Age (years)	**r = -0.47, p_{bonf} = 0.001*** **$p = 7.893\times10^{-5}$**	r = -0.01, p_{bonf} = 1.000 p = 0.931	r = 0.18, p_{bonf} = 1.000 p = 0.147	r = 0.13, p_{bonf} = 1.000 p = 0.299	r = 0.13, p_{bonf} = 1.000 p = 0.306
Education (years)	-	r = -0.10, p_{bonf} = 1.000 p = 0.434	r = -0.22, p_{bonf} = 1.000 p = 0.082	r = 0.12, p_{bonf} = 1.000 p = 0.327	r = -0.07, p_{bonf} = 1.000 p = 0.580
ERQ reappraisal	-	-	r = 0.30, p_{bonf} = 0.237 p = 0.016	r = -0.30, p_{bonf} = 0.262 p = 0.017	r = -0.24, p_{bonf} = 0.834 p = 0.056
ERQ suppression	-	-	-	r = 0.06, p_{bonf} = 1.000 p = 0.636	r = -0.03, p_{bonf} = 1.000 p = 0.789
PSS-10	-	-	-	-	**r = 0.62, $p_{bonf} = 7.815\times10^{-7}$*** **$p = 5.210\times10^{-8}$**

ERQ – Emotion Regulation Questionnaire; PSS-10 – Perceived Stress Scale (10 items); OCI-R – Obsessive-Compulsive Inventory-Revised; *Statistically significant correlations.

The regression model for the ERQ reappraisal score yielded statistical significance ($F_{(6, 56)}$ = 3.53; p = 0.005; R^2 = 0.27). The ERQ reappraisal score was significantly predicted by gender (beta ± standard error = 6.18 ± 2.49; t = 2.48, p = 0.016, standardized beta = 0.33), the ERQ suppression score (0.76 ± 0.22; t = 3.47, p = 0.001, 0.44), and the PSS-10 score (-0.42 ± 0.17; t = -2.40, p = 0.020, -0.38). The regression model for the ERQ suppression score was also statistically significant ($F_{(5, 56)}$ = 4.94; p = 4.000×10^{-4}; R^2 = 0.35). The ERQ suppression score was significantly predicted by gender (-4.93 ± 1.30; t = -3.78, p = 4.000×10^{-4}, -0.45), the ERQ reappraisal score (0.23 ± 0.07; t = 3.47, p = 0.001, 0.40), and the PSS-10 score (0.24 ± 0.10; t = 2.56, p = 0.013, 0.38). **Figure 1** represents the results of both regression models. In conclusion, increased values of ERQ reappraisal were associated with higher ERQ suppression scores. Female participants had higher values in ERQ reappraisal and lower values in ERQ suppression. Elevated values of PSS-10 corresponded to increased scores in ERQ suppression and decreased ERQ reappraisal scores.

For the mediation analysis, the direct effects of OCI-R on ERQ reappraisal (beta ± standard error = -0.06 ± 0.09, p = 0.502) and suppression (-0.06 ± 0.05, p = 0.217) were not statistically significant. Moreover, the indirect effects of OCI-R on ERQ reappraisal (-0.09 ± 0.06, p = 0.116) and suppression (0.06 ± 0.03, p = 0.075) when mediated by PSS-10 were also not statistically significant. Nonetheless, the total effects (combination of direct and indirect effects) were statistically significant for the ERQ reappraisal (-0.16 ± 0.08, p = 0.036) but not for the ERQ suppression score (-4.00×10^{-3} ± 0.04, p = 0.916). Moreover, the ERQ reappraisal and suppression score had a statistically significant association (16.95 ± 5.55, p = 0.002) (Hayes, 2009). **Figure 2** represents the mediation analysis results. In conclusion, the ERQ reappraisal score is explained by the direct effect of the OCI-R score combined with the OCI-R effect mediated by the PSS-10 score. Moreover, the ERQ reappraisal and suppression score influence each other.

5. Discussion

In this study, we evaluated if stress and OC symptoms have a negative effect on emotion regulation measures in a sample composed of OCD and healthy participants. Our main results demonstrated that suppression and reappraisal abilities are predicted by gender and stress levels but not by OC symptoms. Moreover, we observed that the reappraisal score results from a combination of direct effects of OC symptoms and indirect effects mediated by stress levels.

First, our results showed that OCD patients had reduced reappraisal scores in line with past findings (De Wit et al., 2015; Fernández de la Cruz et al., 2013; Fink et al., 2018; Paul et al., 2016; Maria Picó-Pérez et al., 2019; A. L. L. Thorsen et al., 2019; Yazici & Yazici, 2019). However, in contrast with these findings, we did not observe an augmented use of suppression in the OCD group. Most of the patients were under pharmacological treatment. Thus, they might have reduced the use of suppression to attenuate the emotional impact of obsessions and distress. However, the average Y-BOCS score indicates severe to extreme OC symptomatology despite the treatment. Moreover, some authors did not find increased suppression scores (De Wit et al., 2015; Paul et al., 2016; A. L. L. Thorsen et al., 2019) even in OCD patients without medication. In this way, other factors may affect the suppression score in OCD individuals. On the other hand, the control participants included in this study may regularly use suppression strategies given the higher difficulty and cognitive cost in using reappraisal for emotion regulation (Milyavsky et al., 2019; Ortner et al., 2016; Suri et al., 2015). In agreement with this, we found that higher emotion reappraisal abilities were predicted by increased suppression scores and vice versa. Furthermore, there was a positive influence between reappraisal and suppression scores in the mediation analysis. Thus, our results might indicate that effective emotion regulation depends on the use of both strategies. Indeed, past findings showed that the frequent practice of reappraisal is not linked to reduced use of suppression strategies (Moore et al., 2008). Additionally, studies exploring the spontaneous use of emotion regulation strategies showed that reappraisal is not applied more often than suppression (Troy et al., 2018).

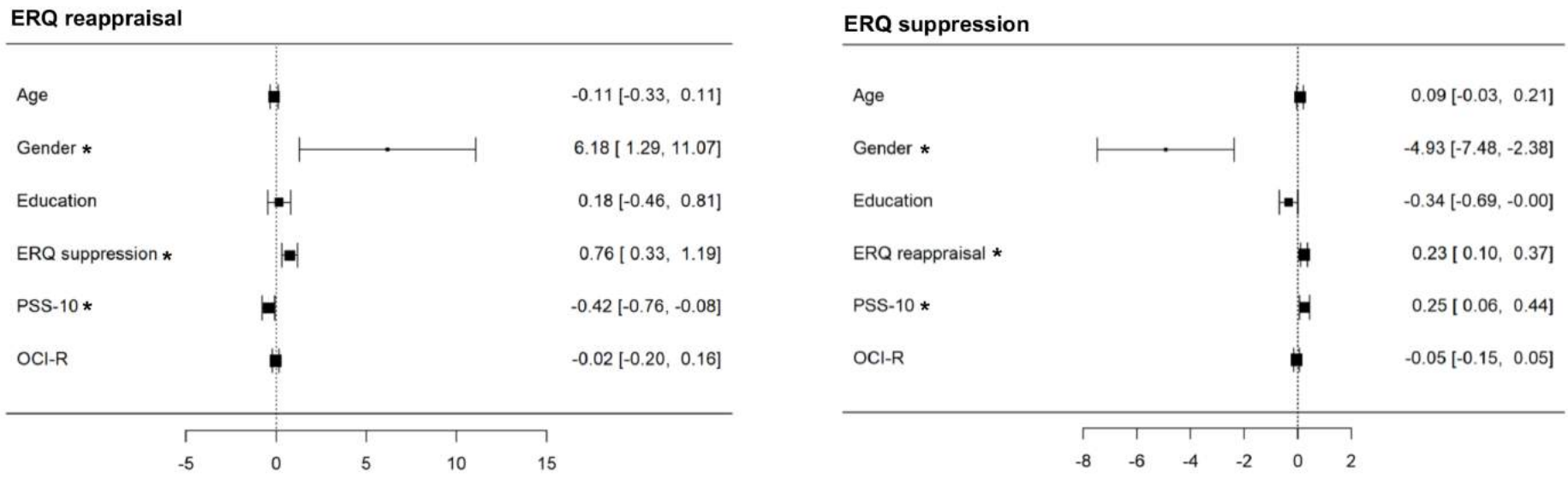


Figure 1 Representation of the estimates and standard error of the predictors for the multiple regression analyses for the ERQ reappraisal and ERQ suppression scores including the total sample. Gender is encoded as male – 0 and female – 1; ERQ – Emotion Regulation Questionnaire; PSS-10 – Perceived Stress Scale (10 items); OCI-R – Obsessive-Compulsive Inventory-Revised; *statistically significant effects.

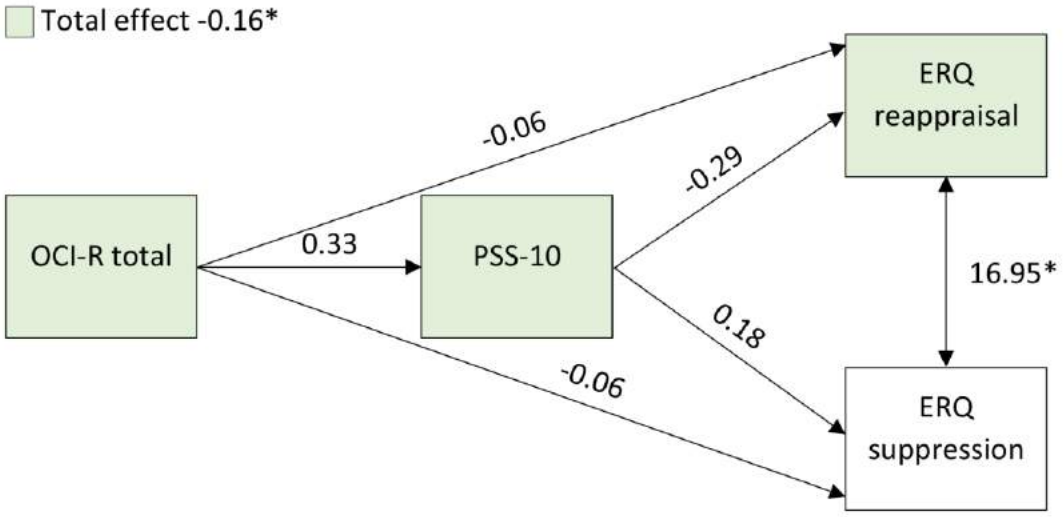


Figure 2 Representation of the mediation analysis results. The values represent the estimates. ERQ – Emotion Regulation Questionnaire; PSS-10 – Perceived Stress Scale (10 items); OCI-R – Obsessive-Compulsive Inventory-Revised; *statistically significant effects.

We also found augmented levels of perceived stress in the OCD group supporting the interplay between OCD and stress (Adams et al., 2018; P. Morgado et al., 2013; Raposo-Lima & Morgado, 2019; Sousa-Lima et al., 2019). This outcome was further reinforced by a strong positive correlation between stress and OC scores in the total sample and the OCD group.

Both the suppression and reappraisal scores were predicted by gender and stress levels but not by the OC score. Moreover, the reappraisal score resulted from a combination of direct effects of OC symptoms and indirect effects of these symptoms mediated by perceived stress levels. Past researchers also reported that women express more their emotions and have more practice at successfully regulating them (Lithari et al., 2010; Webb et al., 2012), while men are culturally shaped to suppress some type of emotions (e.g. sadness and fear) (Berke et al., 2018). Thus, males might have more difficulties in identifying, accepting, and regulating emotions. Moreover, women use suppression strategies less frequently than men (Cutuli, 2014). Consistent with our findings, previous researchers also found that maladaptive strategies (suppression and rumination) and reappraisal were positively and negatively associated with stress symptoms, respectively (Miklósi et al., 2014; Moore et al., 2008). Also, individuals under stressful conditions are more predisposed to the effects of negative emotional stimuli (Kinner et al., 2014; Shermohammed et al., 2017; Tsumura et al., 2015), and are ineffective in distracting themselves (Kinner et al., 2014; Oei et al., 2012) or reappraising their emotions (Raio et al., 2013;

Tsumura et al., 2015) when exposed to affective stimuli. Moreover, stress leads to the engagement of maladaptive strategies such as worry and rumination (Denson et al., 2009). Thus, individuals under stress may be more prone to use suppressing strategies. These findings may result from stress-induced impairment of cognitive processes (e.g. cognitive flexibility and inhibitory and goal-directed behavior) due to the disruption of prefrontal function (Quinn & Joormann, 2020). Thus, stress might inhibit the prefrontal cortical activity hampering the modulation of limbic regions (e.g. amygdala) during emotion regulation (Shermohammed et al., 2017; Nuno Sousa & Almeida, 2012). Indeed, these brain regions are also implicated in emotion regulation processes (Buhle et al., 2014; Kohn et al., 2014). In summary, OCD individuals have elevated stress symptoms that might weaken their ability to use emotion reappraisal. Their cognitive resources are impaired by stress leading to an increased response to negative emotions (Milyavsky et al., 2019). Instead of reappraisal, they may choose more effortless maladaptive strategies (e.g. suppression and compulsions) (Ortner et al., 2016) to regulate their emotions, leading to a rebound effect on distress and anxiety levels (Janeck & Calamari, 1999; Miklósi et al., 2014; Najmi et al., 2009; Naragon-Gainey et al., 2017).

Our findings are limited by the lack of control for anxiety and depression levels. Both OC and stress symptoms are associated with anxious and depressive mood (Goodwin, 2015; N. Sousa, 2016). Yap and colleagues (Yap et al., 2018) found that OCD severity was not associated with emotion regulation deficits when controlling for anxiety and depression scores. Moreover, Moore et al. (2008) found associations between the ERQ scores and anxiety and depression symptoms. Thus, anxiety and depression might have a significant impact on emotion regulation (Maria Picó-Pérez et al., 2017; Schäfer et al., 2017). Our results might have also been affected by the fact that most of the OCD patients selected for this study were medicated and some were frequenting psychotherapy sessions. Moreover, our study has a cross-sectional design hampering the analysis of stress and OC symptoms variations on emotional regulation. Future studies with cognitive behavioral therapy and stress management for OCD might provide further insights. Additionally, our sample had a higher proportion of female individuals. However, the main conclusions were controlled for gender ratio. Finally, our results need to be replicated with larger samples.

This study provides a novel perspective of emotional regulation impairments in OCD. The reliance on suppression strategies and the difficulty in using reappraisal approaches are explained by stress levels and not directly explained by OC symptoms. Our conclusions support the inclusion of stress management in cognitive-behavioral therapy treatments to improve the processes of emotion regulation in OCD patients.

6. Funding

This work has been funded by National funds, through the Foundation for Science and Technology (FCT) - project UIDB/50026/2020 and UIDP/50026/2020; and by the projects NORTE-01-0145-FEDER-000013 and NORTE-01-0145-FEDER-000023, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). This work was additionally supported by a research grant from the Clinical Academic Center, Braga, Portugal ("Treating refractory obsessive-compulsive disorder using real-time functional magnetic resonance imaging neurofeedback"). SF was supported by a combined Ph.D. scholarship from the FCT and the company iCognitus4ALL – IT Solutions, Lda (PD/BDE/127839/2016). MPP was supported by an institutional post-doctoral grant (EMED_BPD_2019_002). RV was supported by an FCT research fellowship (UMINHO/BI/340/2018).

7. References

Abramowitz, J. S., & Deacon, B. J. (2006). Psychometric properties and construct validity of the Obsessive–Compulsive Inventory—Revised: Replication and extension with a clinical sample. Journal of Anxiety Disorders, 20(8), 1016–1035. https://doi.org/10.1016/J.JANXDIS.2006.03.001

Adams, T. G., Kelmendi, B., Brake, C. A., Gruner, P., Badour, C. L., & Pittenger, C. (2018). The Role of Stress in the Pathogenesis and Maintenance of Obsessive-Compulsive Disorder. Chronic Stress, 2(1), 247054701875804. https://doi.org/10.1177/2470547018758043

Aldao, A., & Mennin, D. S. (2012). Paradoxical cardiovascular effects of implementing adaptive emotion regulation strategies in generalized anxiety disorder. Behaviour Research and Therapy, 50(2), 122–130. https://doi.org/10.1016/j.brat.2011.12.004

American Psychiatric Association. (2013). Diagnostic Statistical Manual of Mental Disorders (DSM-5). In American Psychiatric Association (5th, revised ed.). American Psychiatric Association Pub, 2013.

Berke, D. S., Reidy, D., & Zeichner, A. (2018). Masculinity, emotion regulation, and psychopathology: A critical review and integrated model. Clinical Psychology Review, 66(July 2017), 106–116. https://doi.org/10.1016/j.cpr.2018.01.004

Biesanz, J. C., Falk, C. F., & Savalei, V. (2010). Assessing mediational models: Testing and interval estimation for indirect effects. Multivariate Behavioral Research, 45(4), 661–701. https://doi.org/10.1080/00273171.2010.498292

Brander, G., Pérez-Vigil, A., Larsson, H., & Mataix-Cols, D. (2016). Systematic review of environmental risk factors for Obsessive-Compulsive Disorder: A proposed roadmap from association to causation. Neuroscience & Biobehavioral Reviews, 65, 36–62. https://doi.org/10.1016/j.neubiorev.2016.03.011

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., & Ochsner, K. N. (2014). Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. Cerebral Cortex, 24(11), 2981–2990. https://doi.org/10.1093/cercor/bht154

Castro-Rodrigues, P., Camacho, M., Almeida, S., Marinho, M., Soares, C., Barahona-Corrêa, J. B., & Oliveira-Maia, A. J. (2018). Criterion Validity of the Yale-Brown Obsessive-Compulsive Scale Second Edition for Diagnosis of Obsessive-Compulsive Disorder in Adults. Frontiers in Psychiatry, 9(SEP), 1–10. https://doi.org/10.3389/fpsyt.2018.00431

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A Global Measure of Perceived Stress. Journal of Health and Social Behavior, 24(4), 385. https://doi.org/10.2307/2136404

Coles, M. E., Johnson, E. M., & Schubert, J. R. (2011). Retrospective Reports of the Development of Obsessive Compulsive Disorder: Extending Knowledge of the Protracted Symptom Phase. Behavioural and Cognitive Psychotherapy, 39(5), 579–589. https://doi.org/10.1017/S135246581100004X

Cutuli, D. (2014). Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Frontiers in Systems Neuroscience, 8(September), 1–6. https://doi.org/10.3389/fnsys.2014.00175

De Wit, S. J., Van Der Werf, Y. D., Mataix-Cols, D., Trujillo, J. P., Van Oppen, P., Veltman, D. J., & van den Heuvel, O. A. (2015). Emotion regulation before and after transcranial magnetic stimulation in obsessive compulsive disorder. Psychological Medicine, 45(14), 3059–3073. https://doi.org/10.1017/S0033291715001026

Denson, T. F., Spanovic, M., & Miller, N. (2009). Cognitive appraisals and emotions predict cortisol and immune responses: A meta-analysis of acute laboratory social stressors and emotion inductions. Psychological Bulletin, 135(6), 823–853. https://doi.org/10.1037/a0016909

Fernández de la Cruz, L., Landau, D., Iervolino, A. C., Santo, S., Pertusa, A., Singh, S., & Mataix-Cols, D. (2013). Experiential avoidance and emotion regulation difficulties in hoarding disorder. Journal of Anxiety Disorders, 27(2), 204–209. https://doi.org/10.1016/j.janxdis.2013.01.004

Fink, J., Pflugradt, E., Stierle, C., & Exner, C. (2018). Changing disgust through imagery rescripting and cognitive reappraisal in contamination-based obsessive-compulsive disorder. Journal of Anxiety Disorders, 54(January), 36–48. https://doi.org/10.1016/j.janxdis.2018.01.002

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. Psychological Assessment, 14(4), 485–496. https://doi.org/10.1037/1040-3590.14.4.485

Gaab, J., Blättler, N., Menzi, T., Pabst, B., Stoyer, S., & Ehlert, U. (2003). Randomized controlled evaluation of the effects of cognitive–behavioral stress management on cortisol responses to acute stress in healthy subjects. Psychoneuroendocrinology, 28(6), 767–779. https://doi.org/10.1016/S0306-4530(02)00069-0

Goldberg, X., Cardoner, N., Alonso, P., López-Solà, C., Real, E., Hernández-Ribas, R., Jiménez-Murcia, S., Subirà, M., Segalàs, C., Menchón, J. M., & Soriano-Mas, C. (2016). Inter-individual variability in emotion regulation: Pathways to obsessive-compulsive symptoms. Journal of Obsessive-Compulsive and Related Disorders, 11, 105–112. https://doi.org/10.1016/j.jocrd.2016.10.002

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. II. Validity. Archives of General Psychiatry, 46(11), 1012–1016. http://www.ncbi.nlm.nih.gov/pubmed/2510699

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Archives of General Psychiatry, 46(11), 1006–1011. http://www.ncbi.nlm.nih.gov/pubmed/2684084

Goodwin, G. M. (2015). The overlap between anxiety, depression, and obsessive-compulsive disorder. Dialogues in Clinical Neuroscience, 17(3), 249–260.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. Journal of Personality and Social Psychology, 85(2), 348–362. http://www.ncbi.nlm.nih.gov/pubmed/12916575

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. Communication Monographs, 76(4), 408–420. https://doi.org/10.1080/03637750903310360

Janeck, A. S., & Calamari, J. E. (1999). Thought suppression in obsessive-compulsive disorder. Cognitive Therapy and Research, 23(5), 497–509. https://doi.org/10.1023/A:1018720404750

Kim, H. G., Cheon, E. J., Bai, D. S., Lee, Y. H., & Koo, B. H. (2018). Stress and heart rate variability: A meta-analysis and review of the literature. In Psychiatry Investigation (Vol. 15, Issue 3, pp. 235–245). Korean Neuropsychiatric Association. https://doi.org/10.30773/pi.2017.08.17

Kinner, V. L., Het, S., & Wolf, O. T. (2014). Emotion regulation: exploring the impact of stress and sex. Frontiers in Behavioral Neuroscience, 8(November), 1–8. https://doi.org/10.3389/fnbeh.2014.00397

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). NeuroImage Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. NeuroImage, 87, 345–355. https://doi.org/10.1016/j.neuroimage.2013.11.001

Lewis, E. J., Yoon, K. L., & Joormann, J. (2018). Emotion regulation and biological stress responding: associations with worry, rumination, and reappraisal. Cognition and Emotion, 32(7), 1487–1498. https://doi.org/10.1080/02699931.2017.1310088

Lin, H., Katsovich, L., Ghebremichael, M., Findley, D. B., Grantz, H., Lombroso, P. J., King, R. A., Zhang, H., & Leckman, J. F. (2007). Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. Journal of Child Psychology and Psychiatry and Allied Disciplines, 48(2), 157–166. https://doi.org/10.1111/j.1469-7610.2006.01687.x

Lithari, C., Frantzidis, C. A., Papadelis, C., Vivas, A. B., Klados, M. A., Kourtidou-Papadeli, C., Pappas, C., Ioannides, A. A., & Bamidis, P. D. (2010). Are Females More Responsive to Emotional Stimuli? A Neurophysiological Study Across Arousal and Valence Dimensions. Brain Topography, 23(1), 27–40. https://doi.org/10.1007/s10548-009-0130-5

Miklósi, M., Martos, T., Szabó, M., Kocsis-Bogár, K., & Forintos, D. (2014). Cognitive emotion regulation and stress: a multiple mediation approach. Translational Neuroscience, 5(1), 64–71. https://doi.org/10.2478/s13380-014-0207-9

Milyavsky, M., Webber, D., Fernandez, J. R., Kruglanski, A. W., Goldenberg, A., Suri, G., & Gross, J. J. (2019). To reappraise or not to reappraise? Emotion regulation choice and cognitive energetics. Emotion, 19(6), 964–981. https://doi.org/10.1037/emo0000498

Moore, S. A., Zoellner, L. A., & Mollenholt, N. (2008). Are expressive suppression and cognitive reappraisal associated with stress-related symptoms? Behaviour Research and Therapy, 46(9), 993–1000. https://doi.org/10.1016/j.brat.2008.05.001

Morgado, P., Freitas, D., Bessa, J. M., Sousa, N., & Cerqueira, J. J. (2013). Perceived Stress in Obsessive–Compulsive Disorder is Related with Obsessive but Not Compulsive Symptoms. Frontiers in Psychiatry, 4(APR), 21. https://doi.org/10.3389/fpsyt.2013.00021

Morgado, P., Marques, F., Ribeiro, B., Leite-Almeida, H., Pêgo, J. M., Rodrigues, A. J., Dalla, C., Kokras, N., Sousa, N., & Cerqueira, J. J. (2015). Stress induced risk-aversion is reverted by D2/D3 agonist in the rat. European Neuropsychopharmacology, 25(10), 1744–1752. https://doi.org/10.1016/j.euroneuro.2015.07.003

Najmi, S., Riemann, B. C., & Wegner, D. M. (2009). Managing unwanted intrusive thoughts in obsessive-compulsive disorder: Relative effectiveness of suppression, focused distraction, and acceptance. Behaviour Research and Therapy, 47(6), 494–503. https://doi.org/10.1016/j.brat.2009.02.015

Naragon-Gainey, K., McMahon, T. P., & Chacko, T. P. (2017). The structure of common emotion regulation strategies: A meta-analytic examination. Psychological Bulletin, 143(4), 384–427. https://doi.org/10.1037/bul0000093

Oei, N. Y. L., Veer, I. M., Wolf, O. T., Spinhoven, P., Rombouts, S. A. R. B., & Elzinga, B. M. (2012). Stress shifts brain activation towards ventral 'affective' areas during emotional distraction. Social Cognitive and Affective Neuroscience, 7(4), 403–412. https://doi.org/10.1093/scan/nsr024

Ortner, C. N. M., Ste Marie, M., & Corno, D. (2016). Cognitive Costs of Reappraisal Depend on Both Emotional Stimulus Intensity and Individual Differences in Habitual Reappraisal. PLOS ONE, 11(12), e0167253. https://doi.org/10.1371/journal.pone.0167253

Paul, S., Simon, D., Endrass, T., & Kathmann, N. (2016). Altered emotion regulation in obsessive-compulsive disorder as evidenced by the late positive potential. Psychological Medicine, 46(1), 137–147. https://doi.org/10.1017/S0033291715001610

Picó-Pérez, M., Ipser, J., Taylor, P., Alonso, P., López-Solà, C., Real, E., Segalàs, C., Roos, A., Menchón, J. M., Stein, D. J., & Soriano-Mas, C. (2019). Intrinsic functional and structural connectivity of emotion regulation networks in obsessive-compulsive disorder. Depression and Anxiety, 36(2), 110–120. https://doi.org/10.1002/da.22845

Picó-Pérez, M., Moreira, P. S., Ferreira, V. D. M., Radua, J., Mataix-Cols, D., Sousa, N., Soriano-Mas, C., & Morgado, P. (2020). Modality-specific overlaps in brain structure and function in Obsessive-compulsive disorder: multimodal meta-analysis of case-control MRI studies. Neuroscience & Biobehavioral Reviews. https://doi.org/10.1016/j.neubiorev.2020.01.033

Picó-Pérez, M., Radua, J., Steward, T., Menchón, J. M., & Soriano-Mas, C. (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 79(January), 96–104. https://doi.org/10.1016/j.pnpbp.2017.06.001

Quinn, M. E., & Joormann, J. (2020). Executive control under stress: Relation to reappraisal ability and depressive symptoms. Behaviour Research and Therapy, 131(April), 103634. https://doi.org/10.1016/j.brat.2020.103634

Raio, C. M., Orederu, T. A., Palazzolo, L., Shurick, A. A., & Phelps, E. A. (2013). Cognitive emotion regulation fails the stress test. Proceedings of the National Academy of Sciences, 110(37), 15139–15144. https://doi.org/10.1073/pnas.1305706110

Raposo-Lima, C., & Morgado, P. (2019). The Role of Environmental Factors in the Pathogenesis of Obsessive-Compulsive and Related Disorders. In F. L. Fontenelle & M. Yucel (Eds.), A Transdiagnostic Approach to Obsessions, Compulsions and Related Phenomena (p. 452). Cambridge University Press.

https://books.google.pt/books?id=Zqh7DwAAQBAJ&pg=PA39&lpg=PA39&dq=catarina+lima+chapter+stress+obsessive&source=bl&ots=ZPksw8byc0&sig=ACfU3U3gYzgf9NnKCS9f9XgeqkwwNahPkA&hl=pt-PT&sa=X&ved=2ahUKEwijpKW394jqAhUMqxoKHcCID0kQ6AEwAHoECAoQAQ#v=onepage&q=catarina

Schäfer, J. Ö., Naumann, E., Holmes, E. A., Tuschen-Caffier, B., & Samson, A. C. (2017). Emotion Regulation Strategies in Depressive and Anxiety Symptoms in Youth: A Meta-Analytic Review. Journal of Youth and Adolescence, 46(2), 261–276. https://doi.org/10.1007/s10964-016-0585-0

Shermohammed, M., Mehta, P. H., Zhang, J., Brandes, C. M., Chang, L. J., & Somerville, L. H. (2017). Does Psychosocial Stress Impact Cognitive Reappraisal? Behavioral and Neural Evidence. Journal of Cognitive Neuroscience, 29(11), 1803–1816. https://doi.org/10.1162/jocn_a_01157

Sousa-Lima, J., Moreira, P. S., Raposo-Lima, C., Sousa, N., & Morgado, P. (2019). Relationship between obsessive compulsive disorder and cortisol: Systematic review and meta-analysis. European Neuropsychopharmacology, 29(11), 1185–1198. https://doi.org/10.1016/j.euroneuro.2019.09.001

Sousa, N. (2016). The dynamics of the stress neuromatrix. Molecular Psychiatry, 21(3), 302–312. https://doi.org/10.1038/mp.2015.196

Sousa, Nuno, & Almeida, O. F. X. (2012). Disconnection and reconnection: the morphological basis of (mal)adaptation to stress. Trends in Neurosciences, 35(12), 742–751. https://doi.org/10.1016/j.tins.2012.08.006

Suri, G., Whittaker, K., & Gross, J. J. (2015). Launching reappraisal: It's less common than you might think. Emotion, 15(1), 73–77. https://doi.org/10.1037/emo0000011

Thorsen, A. L., de Wit, S. J., de Vries, F. E., Cath, D. C., Veltman, D. J., van der Werf, Y. D., Mataix-Cols, D., Hansen, B., Kvale, G., & van den Heuvel, O. A. (2019). Emotion Regulation in Obsessive-Compulsive Disorder, Unaffected Siblings, and Unrelated Healthy Control Participants. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4(4), 352–360. https://doi.org/10.1016/j.bpsc.2018.03.007

Trigo, M., Canudo, N., Branco, F., & Silva, D. (2010). Estudo das propriedades psicométricas da Perceived Stress Scale (PSS) na população portuguesa. Psychologica, 10(53), 353–378. http://iduc.uc.pt/index.php/psychologica/article/view/1093

Troy, A. S., Shallcross, A. J., Brunner, A., Friedman, R., & Jones, M. C. (2018). Cognitive reappraisal and acceptance: Effects on emotion, physiology, and perceived cognitive costs. Emotion, 18(1), 58–74. https://doi.org/10.1037/emo0000371

Tsumura, H., Sensaki, J., & Shimada, H. (2015). Stress-induced cortisol is associated with generation of non-negative interpretations during cognitive reappraisal. BioPsychoSocial Medicine, 9(1), 23. https://doi.org/10.1186/s13030-015-0049-x

Vaz, F. M., Martins, C., & Martins, E. C. (2014). Diferenciação emocional e regulação emocional em adultos portugueses. PSICOLOGIA, 22(2), 123. https://doi.org/10.17575/rpsicol.v22i2.350

Visted, E., Sørensen, L., Osnes, B., Svendsen, J. L., & Binder, P. (2017). The Association between Self-Reported Difficulties in Emotion Regulation and Heart Rate Variability : The Salient Role of Not Accepting Negative Emotions. 8(March), 1–9. https://doi.org/10.3389/fpsyg.2017.00328

Webb, T. L., Miles, E., & Sheeran, P. (2012). Dealing with feeling: A meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. Psychological Bulletin, 138(4), 775–808. https://doi.org/10.1037/a0027600

Yap, K., Mogan, C., Moriarty, A., Dowling, N., Blair-West, S., Gelgec, C., & Moulding, R. (2018). Emotion regulation difficulties in obsessive-compulsive disorder. Journal of Clinical Psychology, 74(4), 695–709. https://doi.org/10.1002/jclp.22553

Yazici, K. U., & Yazici, I. P. (2019). Decreased theory of mind skills, increased emotion dysregulation and insight levels in adolescents diagnosed with obsessive compulsive disorder. Nordic Journal of Psychiatry, 73(7), 462–469. https://doi.org/10.1080/08039488.2019.1652341

Zaehringer, J., Jennen-Steinmetz, C., Schmahl, C., Ende, G., & Paret, C. (2020). Psychophysiological Effects of Downregulating Negative Emotions: Insights From a Meta-Analysis of Healthy Adults. Frontiers in Psychology, 11(April). https://doi.org/10.3389/fpsyg.2020.00470

Zilverstand, A., Parvaz, M. A., & Goldstein, R. Z. (2017). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. NeuroImage, 151(8), 105–116. https://doi.org/10.1016/j.neuroimage.2016.06.009

8. Supplementary material

Table S1 Results of Pearson's correlation among demographic and psychometric variables for the obsessive-compulsive group (p_{bonf} - p-value after Bonferroni correction).

	Education (years)	ERQ reappraisal	ERQ suppression	PSS-10	OCI-R total
Age (years)	r = -0.43, p_{bonf} = 0.073 p = 0.005	r = -0.04, p_{bonf} = 1.000 p = 0.818	r = 0.28, p_{bonf} = 1.000 p = 0.075	r = 0.05, p_{bonf} = 1.000 p = 0.758	r = 0.03, p_{bonf} = 1.000 p = 0.867
Education (years)	-	r = -0.11, p_{bonf} = 1.000 p = 0.476	r = -0.28, p_{bonf} = 1.000 p = 0.073	r = 0.13, p_{bonf} = 1.000 p = 0.403	r = -0.11, p_{bonf} = 1.000 p = 0.491
ERQ reappraisal	-	-	r = 0.18, p_{bonf} = 1.000 p = 0.257	r = -0.39, p_{bonf} = 0.154 p = 0.010	r = -0.23, p_{bonf} = 1.000 p = 0.135
ERQ suppression	-	-	-	r = 0.03, p_{bonf} = 1.000 p = 0.854	r =- 0.01, p_{bonf} = 1.000 p = 0.935
PSS-10	-	-	-	-	**r = 0.55, p_{bonf} = 0.003*** **p = 2.000×10^{-4}**

ERQ – Emotion Regulation Questionnaire; PSS-10 – Perceived Stress Scale (10 items); OCI-R – Obsessive-Compulsive Inventory-Revised; *Statistically significant correlations.

Table S2 Results of Pearson's correlation among demographic and psychometric variables for the control group (p_{bonf} - p-value after Bonferroni correction).

	Education (years)	ERQ reappraisal	ERQ suppression	PSS-10	OCI-R total
Age (years)	r = -0.56, p_{bonf} = 0.097 p = 0.006	r = 0.09, p_{bonf} = 1.000 p = 0.688	r = 0.05, p_{bonf} = 1.000 p = 0.809	r = 0.25, p_{bonf} = 1.000 p = 0.265	r = 0.24, p_{bonf} = 1.000 p = 0.294
Education (years)	-	r = -0.04, p_{bonf} = 1.000 p = 0.871	r = -0.11, p_{bonf} = 1.000 p = 0.619	r = 0.07, p_{bonf} = 1.000 p = 0.743	r = -0.04, p_{bonf} = 1.000 p = 0.858
ERQ reappraisal	-	-	r = 0.54, p_{bonf} = 0.144 p = 0.010	r = 0.24, p_{bonf} = 1.000 p = 0.272	r = 0.18, p_{bonf} = 1.000 p = 0.426
ERQ suppression	-	-	-	r = 0.22, p_{bonf} = 1.000 p = 0.320	r =0.02, p_{bonf} = 1.000 p = 0.919
PSS-10	-	-	-	-	r = 0.48, p_{bonf} = 0.420 p = 0.028

ERQ – Emotion Regulation Questionnaire; PSS-10 – Perceived Stress Scale (10 items); OCI-R – Obsessive-Compulsive Inventory-Revised.

CHAPTER III

Reduced hedonic valuation of rewards and unaffected cognitive regulation in chronic stress

Sónia Ferreira*, Carlos Veiga*, Pedro Moreira, Ricardo Magalhães, Ana Coelho, Paulo Marques, Carlos Portugal-Nunes, Nuno Sousa, Pedro Morgado

Article published in Frontiers in Neuroscience, 22 Nov 2019

DOI: 10.3389/fnins.2019.00724

Link: https://www.frontiersin.org/articles/10.3389/fnins.2019.00724/full

*Equal contribution

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 10 July 2019
doi: 10.3389/fnins.2019.00724

Reduced Hedonic Valuation of Rewards and Unaffected Cognitive Regulation in Chronic Stress

*Sónia Ferreira[1,2†], Carlos Veiga[1,2†], Pedro Moreira[1,2], Ricardo Magalhães[1,2], Ana Coelho[1,2], Paulo Marques[1,2], Carlos Portugal-Nunes[1,2], Nuno Sousa[1,2,3] and Pedro Morgado[1,2,3]**

[1] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal, [2] ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal, [3] Clinical Academic Center – Braga, Braga, Portugal

Cognition can influence choices by modulation of decision-making processes. This cognitive regulation is defined as processing information, applying knowledge, and changing preferences to consciously modulate decisions. While cognitive regulation of emotions has been extensively studied in psychiatry, few works have detailed cognitive regulation of decision-making. Stress may influence emotional behavior, cognition, and decision-making. In addition, the brain regions responsible for decision-making are sensitive to stress-induced changes. Thus, we hypothesize that chronic stress may disrupt the ability to regulate choices. Herein, we used a functional magnetic resonance imaging task where fourteen control and fifteen chronically stressed students had to cognitively upregulate or downregulate their craving before placing a bid to obtain food. We found that stressed participants placed lower bids to get the reward and chose less frequently higher bid values for food. Nevertheless, we did not find neural and behavioral differences during cognitive regulation of craving. Our outcomes revealed that chronic stress impacts decision-making after cognitive regulation of craving by reducing the valuation of food rewards but not cognitive modulation itself. Importantly, our results need further validation with larger sample sizes.

Keywords: stress, decision-making, cognition, magnetic resonance imaging, fMRI, reward, human, food

OPEN ACCESS

Edited by:
Ruolei Gu,
Institute of Psychology (CAS), China

Reviewed by:
Sunny Dutra,
William James College, United States
Claire Zedelius,
University of California, Santa Barbara, United States

***Correspondence:**
Pedro Morgado
pedromorgado@med.uminho.pt

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Decision Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *15 February 2019*
Accepted: *28 June 2019*
Published: *10 July 2019*

Citation:
Ferreira S, Veiga C, Moreira P, Magalhães R, Coelho A, Marques P, Portugal-Nunes C, Sousa N and Morgado P (2019) Reduced Hedonic Valuation of Rewards and Unaffected Cognitive Regulation in Chronic Stress. Front. Neurosci. 13:724. doi: 10.3389/fnins.2019.00724

INTRODUCTION

Value-based decision-making is the ability to make a choice from competing courses of action/alternatives based on subjective values and possible outcomes attributed to them (Balleine, 2005). This process is carried out whenever a person chooses from different alternatives (e.g., choosing between eating an apple or an orange, or between going out or not). Different interacting systems are responsible for the valuation and action selection processes in the brain (Rangel et al., 2008). First, a valuation system computes the action values. A comparator system needs to evaluate the action values. An accumulator system receives and accumulates the value signals from the

Abbreviations: ACTH, adrenocorticotropic hormone; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; dlPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; GLM, general linear model; MNI, Montreal Neurological Institute; PSS-10, 10-items Perceived Stress Scale; vmPFC, ventromedial prefrontal cortex.

comparator system until the signal for one of the actions is sufficiently strong for the choice to be executed (Gold and Shadlen, 2007; Basten et al., 2010).

Values assigned to actions during the valuation process can be influenced by different factors such as the degree of risk or uncertainty of the action (Platt and Huettel, 2008; Rangel et al., 2008). Humans have a natural aversion to risky or uncertain choices and place less value on actions with temporal uncertain rewards or multiple sets of outcomes (Christopoulos et al., 2009; McGuire and Kable, 2012). Individuals often place higher values on immediate rewards rather than on future ones (Rangel et al., 2008). Social competition, cooperation, and concerns for the well-being of others also influence decision-making (Fehr and Camerer, 2007). Cognition can also influence choices through modulation of the decision-making processes. This cognitive regulation process may be defined as processing information, applying knowledge and changing preferences to consciously modulate our decisions. While cognitive regulation of emotional response has been extensively studied (Ochsner et al., 2004; Delgado et al., 2008; Wager et al., 2008), few works have detailed cognitive regulation of decision-making. A functional magnetic resonance imaging (fMRI) study where participants had to modulate their cravings for food showed that cognitive regulation affects decision-making through valuation regulation and behavioral control (Hutcherson et al., 2012). The ventromedial prefrontal cortex (vmPFC) is known to compute the value signal of decisions while the dorsolateral prefrontal cortex (dlPFC) modulates this signal during cognitive regulation tasks (Hare et al., 2009, 2011; Kober et al., 2010).

Cognitive regulation of both emotion and decision-making has a role in the treatment of several conditions (schizophrenia, bipolar disorder, depression, obesity, addiction, obsessive-compulsive disorder, and eating disorders) where emotional processing and decision-making are often impaired (Phillips et al., 2003; Ochsner et al., 2004). On the other hand, mental disorders such as schizophrenia, bipolar disorder, post-traumatic stress disorder, and depression are often associated with prolonged exposure to stress (Arnsten, 2015; Sousa, 2016). Stress impacts emotional processing leading to depressive and anxious behavior associated with alterations in amygdala-ventromedial-prefrontal pathways. Moreover, stress elicits cognitive impairments namely working memory and attentional deficits, poor decision-making (e.g., decreased reward sensitivity or increased influence of immediate rewards), behavioral inflexibility, and learning deficits. These cognitive differences are associated with changes in prefrontal and hippocampal regions (Sandi, 2013; Arnsten, 2015; Chen and Baram, 2016; Sousa, 2016). Additionally, the brain regions implicated in decision-making processes are sensitive to stress-induced changes. In fact, changes in fronto-striatal networks involved in behavioral decisions have been reported in both humans and rodents after chronic stress (Dias-Ferreira et al., 2009; Soares et al., 2012; Morgado et al., 2012, 2015a; Sousa, 2016; Magalhães et al., 2018). Thus, stress seems to influence the quality of decisions (Starcke and Brand, 2012; Morgado et al., 2015b; Bryce and Floresco, 2016; Chen and Baram, 2016) because cognitive control is diminished (Yu, 2016).

Stress has also an impact on appetite and eating behavior (Ans et al., 2018) and is one of the factors for development of eating and obesity-associated conditions (Razzoli et al., 2017). Usually, the production of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland leads to the release of cortisol in the adrenal cortex to stimulate hunger and feeding behavior. High cortisol levels are associated with high insulin concentrations resulting in increased caloric intake or food craving (Adam and Epel, 2007). Stress might boost these pathways leading to an increase in food intake and appetite for high-caloric food, or also reduced reward sensitivity to low-caloric food (Razzoli et al., 2017; Ans et al., 2018; Berg Schmidt et al., 2018; Ferrer-Cascales et al., 2018), in agreement with previous stress decision-making studies demonstrating decreased reward sensitivity or increased influence of immediate rewards (Morgado et al., 2015b). Thus, stress seems to be associated with increased food reward sensitivity due to diminished self-control during food choice associated with decreased functional connectivity between the vmPFC and dlPFC (Neseliler et al., 2017) and increased connectivity between the vmPFC and subcortical regions (amygdala and striatum) (Tryon et al., 2013; Maier et al., 2015).

Herein, we used an fMRI task to clarify the impact of chronic stress on cognitive regulation of decisions. Our task consisted of cognitively upregulating or downregulating craving before placing a bid to obtain food. In addition to brain responses, we analyzed behavioral parameters (food valuation score and reaction time) associated with the task, and blood hormonal changes after the task (insulin, cortisol, and glucose). Regarding the previous findings, we hypothesize that chronic stress may disrupt the ability of individuals to regulate their choices. We expect that cognitive regulation deficits after chronic stress manifest by changes in the prefrontal cortex (vmPFC and dlPFC). Subsequently, these deficits lead to decision-making impairments, namely increased reward sensitivity, underlying brain response alterations in prefrontal and striatal regions. Moreover, we expect that chronic stress participants present augmented levels of insulin, glucose, and cortisol after the stimulation with food pictures due to an increased reward sensitivity to food.

MATERIALS AND METHODS

Subjects

We enrolled in this study medical students from the School of Medicine of University of Minho, Portugal. All students were healthy Caucasians, right-handed, and had a healthy body-mass index. One group was under normal academic activities [control group, $n = 14$; 9 females/5 males; median (range) 23.00 (3.00) years of age; education 17.00 (3.00) years] and the other included subjects on the long period of preparation for the medical licensing exam [chronic psychosocial stress condition; stress group, $n = 15$; 10 females/5 males; 24.00 (3.00) years of age; education 18.00 (0.00) years]. This work was conducted 1 to 3 months before the exam, but students usually start preparing 1 year before the exam. Subjects were eligible if they were at least

18 years old, reported no history of psychiatric or neurological conditions, traumatic brain lesion, or substance abuse, and were not on any psychiatric medication. The groups were matched for gender (chi-squared test $\chi^2_{(1)} = 0.02$, $p = 0.893$) but not for age (Mann–Whitney test $U = 169.00$, $p = 0.004$, effect size $r = 0.56$) and education level ($U = 210.00$, $p = 2.579 \times 10^{-8}$, $r = 0.93$).

Ethics Statement

The study was performed in accordance with the Declaration of Helsinki and was approved by Ethics Subcommittee for the Life and Health Sciences of University of Minho, Portugal, and by the Ethics Committee of the Hospital of Braga, Portugal. All subjects were provided with written informed consent following description of the study goals and procedures.

Sociodemographic and Psychological Scales

Subjects filled a questionnaire to characterize gender, age, educational level, handedness, and ethnic origin. Weight and height were also measured to prevent the inclusion of participants with an unhealthy body mass index. Subjects were assessed with the 10-items Perceived Stress Scale (PSS-10) (Cohen et al., 1983; Morgado et al., 2013), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), and the Beck Depression Inventory (BDI) (Beck et al., 1996). PSS-10 measures the extent to which participants perceived their life as unpredictable, uncontrollable, and overloaded during the previous month. The higher the score, the greater the intensity of perceived stress. BAI measures the severity of an individual's anxiety during the previous week. Scores lower than 8 indicate minimal anxiety. Scores higher than 7, 15, and 25 indicate mild, moderate, and severe anxiety, respectively. BDI measures the severity of depression and can be used as a screening tool. Scores lower than 14 indicate minimal depression. Higher scores indicate more severe depressive symptoms.

Blood Sampling and Analysis

Before the fMRI acquisition, samples of venous blood were collected from all participants into a 5 mL potassium ethylenediaminetetraacetic acid tube and a serum tube. We repeated the collection immediately after the fMRI acquisition. Pre-scan blood samples were used to measure cortisol, glucose, insulin, and ACTH serum levels. In post-scan samples, we repeated cortisol, glucose, and insulin serum measurements (ACTH measurement was not repeated due to technical constraints). The collection took place between 2 and 7 pm which assures small variation in cortisol levels during this period (Minkley and Kirchner, 2012). ACTH was measured based on solid-phase, two-site sequential chemiluminescent immunometric assay, and insulin with solid-phase, enzyme-labeled chemiluminescent immunometric assay (IMMULITE 2000, Siemens AG, Germany). Cortisol levels were assessed with competitive immunoassay based on direct chemiluminescent (ADVIA Centaur and Centaur XP, Siemens AG, Germany). Glucose was measured based on the hexokinase-glucose-6-phosphate method (Dimension Vista, Siemens AG, Germany). Standard procedures were applied following the manufacturer instructions.

Statistical Analysis

Data related with psychological scales, laboratory values, and behavioral parameters were analyzed using IBM SPSS Statistics (version 24.0; IBM Corporation, United States). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess for normality in the distribution of data. Comparisons between groups were carried out by parametric *t*-tests or repeated measures ANOVA (*F*-test, with Bonferroni correction for multiple comparisons for *post hoc* tests], or non-parametric Mann-Whitney *U*-tests. Differences were considered statistically significant if $p < 0.05$. Effect sizes were calculated for all statistically significant results.

fMRI Task

The task was adapted from Hutcherson et al. (2012). Subjects were instructed to fast for at least 4 h before their arrival and to eat a light meal before the fasting period to increase the valuation of food pictures. We also informed that they would remain in the laboratory for 30 min at the end of the experiment to eat the food they obtained during the fMRI task. The task consisted of two parts: a pre-scan rating task that provided us with a measure of the baseline value for food, and an in-scan bidding and regulation task that measured the food value under the influence of regulation.

During the pre-scan rating task, subjects were shown 150 pictures of different snack food items (e.g., cake, chips, and candy) and rated, at their own pace, how much they would like to eat them using a four-point scale (1, "Don't want it at all"; 4, "Want it a lot"). Our set of pictures was adapted to the Portuguese context of food.

Afterward, subjects received instructions for the in-scan bidding and regulation task (**Figure 1**). The 150 snack food pictures were shown again, separated into three trial conditions: indulge, distance, and natural. Each type of trial appeared 50 times, randomly interspersed over the scanning run. On each trial, before the food appeared, participants saw an abstract black-and-white symbol indicating the trial type (cue, 2 s). On indulge trials, subjects were instructed to try to increase their craving for the snack using any strategy they needed to. During distance trials, the instruction consisted on trying to decrease their craving. On natural trials, they had to allow thoughts and feelings to come naturally. Subjects had 4 s to look at the item and engage in the craving cognitive regulation task (hereinafter referred as cognitive regulation task). After the 4 s, subjects had 2 s to place a bid (0 €, 1 €, 2 €, or 3 €) for the right to eat that food at the end of the experiment. They were asked to treat each trial as if it were the only decision that counted. These bids allowed us to measure values expressed in behavior at the time of choice.

At the end of the experiment, food was auctioned using an adapted version of the Becker-DeGroot-Marschak auction (Becker et al., 1964; Plassmann et al., 2007). We gave 3 € to each subject to spend during the auction over a maximum of three trials. Snacks and snacks prices were randomly selected by drawing a paper from a bag. The bids on those trials during the fMRI task determined whether subjects got to eat that food.

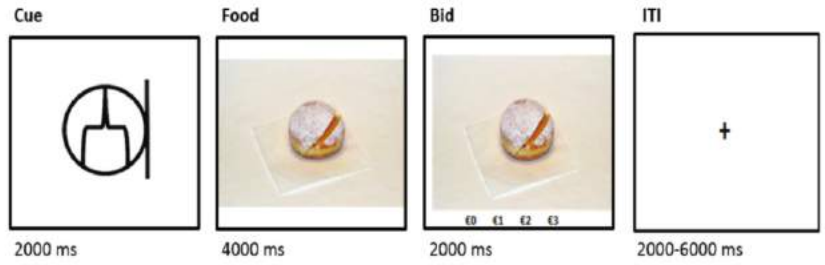


FIGURE 1 | Timing and structure of a trial from the functional magnetic resonance task. ITI, intertrial interval.

Consider b the bid made by the subject during the fMRI task. During the auction, a random price a was drawn (0 €, 1 €, 2 €, and 3 € were chosen with equal probability). If $b \geq a$, the participant got the item and spend a. If $b < a$, the subject did not get the item. The rules of the auction ensure the subjects' best strategy to bid their true value for each food. This was explained and emphasized during the instruction period. For auction effects, omissions resulted in a bid of 0 €.

fMRI Data Acquisition

Each participant was scanned on a clinical approved 1.5 T Siemens Magnetom Avanto system (Siemens Medical Solutions, Germany) using a 12-channel receive-only head array coil. For the functional acquisition, a T2* weighted echo-planar imaging acquisition was acquired: 38 interleaved axial slices, repetition time 2750 ms, echo time 30 ms, field of view 224 mm × 224 mm, flip angle 90°, in-plane resolution 3.5 mm × 3.5 mm, slice thickness 3.5 mm, and between-slice gap 0.5 mm. To optimize the sensitivity in the orbitofrontal cortex, a tilted acquisition in an oblique orientation of 30° relative to the anterior-posterior commissure line was used. In total, 650 volumes were acquired during the task. The task stimulus was presented using the fully integrated fMRI system IFIS-SA (Invivo Corporation, United States) and the same system was used to record the subject key-press responses. One high-resolution T1-weighted Magnetization-Prepared Rapid Acquisition with Gradient Echo sequence, with 1 mm × 1 mm × 1 mm voxel size, repetition time 2.73 s, echo time 3.48 ms, flip angle 7°, field of view 234 mm × 234 mm, and 176 slices was acquired. This anatomical sequence was used to project the functional maps.

fMRI Data Preprocessing

The functional scans from each participant were preprocessed using the Statistical Parametric Mapping (SPM) version 12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, United Kingdom) using MATLAB version R2018a (The MathWorks Inc.,United States). The preprocessing procedures included: slice-timing correction using the first slice as reference; realignment to the mean volume of the acquisition; nonlinear spatial normalization to Montreal Neurological Institute (MNI) standard space and resampling to 2 mm × 2 mm × 2 mm voxel size; spatial smoothing with a 8 mm full-width at half-maximum Gaussian kernel; high pass temporal filtering at 128 s. Participants with more than 3 mm of movement (1 voxel) were excluded ($n = 0$).

fMRI Data Analysis

For the first-level analysis, one general linear model (GLM) was computed per participant. For this GLM, the regressors of interest included: the type of cognitive regulation trial (1 – distance, 2 – natural, and 3 – indulge) and the corresponding bid (4 – bids after distance trials, 5 – bids after natural trials, and 6 – bids after indulge trials). The bid regressors were parametrically modulated by the bid value (0, 1, 2, and 3 €), the pre-rating score before the task (1 to 4), and the reaction time. Additional regressors included: 7 – the cue; 8 – the interstimulus interval; 9 – the omission bids; 10 – 16 the motion parameters estimated during the realignment step. The onset and duration of the regressors were defined accordingly to the stimulus represented in **Figure 1** with a boxcar function and the regressors were convolved with the canonical hemodynamic response function.

At the group level (second-level analysis), a random-effects analysis was performed using four different mixed-design ANOVA models: (1) represented the cognitive regulation during the task (enabled comparisons in average activation for each regulation trial between and within groups); (2) concerned the bidding/valuation during the task modulated by the bid value; (3) concerned the bidding/valuation during the task modulated by the pre-rating score; (4) concerned the bidding/valuation during the task modulated by the reaction time. Models (2) – (4) were used to test if food valuation was different between groups after distinct regulation trials. For all models, the group (stress vs. control) was introduced as the between-subject factor and each trial during cognitive regulation (distance vs. natural vs. indulge) as the within-subject factor. Age and education were used as covariates for all models. All models were implemented with the GLMFlex toolbox[1] which uses partitioned error terms for within-group and between-group comparisons, enabling the estimation of all the effects of interest with a single model.

Results were considered statistically significant after correcting for multiple comparisons using cluster correction

[1]http://nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/GLM_Flex.html

(minimum cluster size of 90 voxels). The minimum cluster size was determined with 3DClustSim (AFNI version 17.0.13; National Institute of Mental Health)[2]. This program determines a minimum cluster size with Monte Carlo Simulation to achieve a corrected significance of $p < 0.05$ with an initial voxel-wise threshold of $p < 0.001$. The Automated Anatomical Labeling plugin for SPM was used to classify the brain regions.

RESULTS

Psychological Assessment

The stress group revealed higher levels of perceived stress (mean ± standard deviation 15.07 ± 5.23) than the control group (8.64 ± 5.27) as assessed by PSS-10 [$t_{(27)} = 3.30$, $p = 0.003$, effect size $d = 1.27$]. No statistically significant differences were found for BAI ($U = 117.50$, $p = 0.591$) and BDI ($U = 134.00$, $p = 0.217$) between groups.

Blood Sampling

The ACTH levels before the fMRI session were similar between the two groups ($U = 81.50$, $p = 0.310$).

Cortisol serum levels were not statistically significantly different between groups [group $F_{(1,27)} = 0.45$, $p = 0.509$] nor within group before and after the fMRI session [group × time $F_{(1,27)} = 1.00 \times 10^{-3}$, $p = 0.971$]. However, cortisol levels decreased in both groups after the task [time $F_{(1,27)} = 10.08$, $p = 0.004$, effect size $\chi^2 = 0.27$].

Glucose serum levels were not statistically significantly different between groups [group $F_{(1,27)} = 0.40$, $p = 0.531$] and the pre and post-measurement were similar within groups [group × time $F_{(1,27)} = 0.18$, $p = 0.672$]. However, glucose levels decreased in both groups after the task [time $F_{(1,27)} = 8.44$, $p = 0.007$, $\chi^2 = 0.24$].

Insulin serum levels were not statistically significantly different between groups [group $F_{(1,27)} = 0.42$, $p = 0.522$] and the pre and post-measurement were similar within groups [group × time $F_{(1,27)} = 3.68$, $p = 0.066$]. However, insulin levels decreased in both groups after the task [time $F_{(1,27)} = 9.21$, $p = 0.005$, $\chi^2 = 0.25$].

Behavioral Analysis

Given the differences in age and education between groups, we used these variables as covariates when analyzing behavioral parameters.

We analyzed the reaction time between and within groups during the different regulation trials (distance, natural, and indulge). We found an interaction effect between the group and the reaction time across the different regulation conditions [group × condition $F_{(2,50)} = 4.00$, $p = 0.024$, $\chi^2 = 0.14$; **Table 1** represents the results for all between and within group factors and covariate effects]. *Post hoc* tests with repeated measures ANOVA demonstrated statistically significant reaction time differences within the control group [$F_{(1.42,18.43)} = 7.06$, $p = 0.010$, $\chi^2 = 0.35$, Greenhouse-Geisser correction for non-sphericity] and within the stress group [$F_{(1.34,18.82)} = 4.72$, $p = 0.033$, $\chi^2 = 0.25$, Greenhouse-Geisser correction for non-sphericity]. Paired *t*-tests with Bonferroni correction showed that the reaction time for natural trials was shorter than for distance [$t_{(13)} = 4.82$, $p = 0.001$, $d = 2.67$] and indulge trials [$t_{(13)} = 3.07$, $p = 0.027$, $d = 1.70$], and distance and indulge trials presented similar reaction times [$t_{(13)} = 1.00$, $p = 1.000$] in the control group. However, we did not find significant statistical differences in the stress group during post-hoc analysis [$1.00 \leq t_{(14)} \leq 2.36$, $0.099 \leq p \leq 1.000$] (**Figure 2**).

Taking into account that different instructions were given during the pre-rating (how much the participants want the food) and the bidding (how much the participants want to pay for the food), we separately analyzed differences between groups in the valuation score across the regulation conditions (distance, natural, and indulge) for pre and post-regulation scores (**Table 1** represents the results for all between and within group factors and covariate effects). During pre-rating, we did not find statistically significant differences between groups or within group in terms of food valuation across the conditions. Moreover, the valuation score varied similarly among the conditions for both groups. However, during bidding, we found differences between groups [group $F_{(1,25)} = 6.91$, $p = 0.014$, $\chi^2 = 0.22$] but not within group in terms of food valuation across the conditions. Moreover, the valuation score varied similarly among the conditions for both groups. The stress group had lower valuation scores (1.06 ± 0.36 €) during bidding in comparison to the control group (1.50 ± 0.36 €) (**Figure 3**).

Moreover, we also studied differences between groups in the number of responses for each bidding value after each cognitive regulation trial inside the scanner. We found a significant interaction effect between the group and the bid value [group × valuation $F_{(2.13,53.15)} = 3.89$, $p = 0.024$, $\chi^2 = 0.13$, Greenhouse-Geisser correction for non-sphericity; **Table 1** represents the results for all between and within group factors and covariate effects]. *Post hoc* tests with repeated measures ANOVA demonstrated that the control [$F_{(3,39)} = 9.61$, $p = 7.000 \times 10^{-5}$, $\chi^2 = 0.42$] and the stress group [$F_{(2.03,28.43)} = 9.04$, $p = 0.001$, $\chi^2 = 0.39$, Greenhouse-Geisser correction for non-sphericity] had a different number of responses across the bid values. Paired *t*-tests with Bonferroni correction demonstrated that on average the stress participants bided more often 0 [$t_{(14)} = 3.93$, $p = 0.009$, $d = 1.78$] and 1 € [$t_{(14)} = 3.38$, $p = 0.027$, $d = 1.81$] than 3 €, while control subjects bided more times 1 [$t_{(13)} = 3.94$, $p = 0.010$, $d = 2.18$] and 2 € [$t_{(13)} = 5.91$, $p = 3.090 \times 10^{-4}$, $d = 3.28$] than 3 € (**Figure 4**).

Neuroimaging Results

We tested for differences in blood-oxygen-level-dependent responses between stress and control groups during each cognitive regulation period/trial (natural, indulge, and distance) – model (1). No statistically significant brain regions were identified for overall differences between groups (main effect of group). When looking at the interaction effect between

[2]https://afni.nimh.nih.gov/

TABLE 1 | Results for statistical tests on behavioral variables associated with the functional magnetic resonance imaging task: reaction time, valuation score, and response frequency.

Statistical effect	Test value	*P*-value	Effect size χ^2
Reaction time			
Condition (distance, natural, and indulge)	$F_{(2,50)} = 3.00$	0.059	
Group × condition	$F_{(2,50)} = 4.00$	0.024	0.14*
Group	$F_{(1,25)} = 0.02$	0.886	
Age	$F_{(1,25)} = 1.36 \times 10^{-4}$	0.991	
Education	$F_{(1,25)} = 0.40$	0.535	
Valuation score			
Pre-rating score			
Condition (distance, natural, and indulge)	$F_{(2,50)} = 1.21$	0.308	
Group × condition	$F_{(2,50)} = 0.85$	0.433	
Group	$F_{(1,25)} = 0.32$	0.574	
Age	$F_{(1,25)} = 0.03$	0.873	
Education	$F_{(1,25)} = 0.12$	0.728	
Bid value			
Condition (distance, natural, and indulge)	$F_{(1.32,33.03)} = 0.57$	0.502	
Group × condition	$F_{(1.32,33.03)} = 1.87$	0.180	
Group	$F_{(1,25)} = 6.91$	0.014	0.22*
Age	$F_{(1,25)} = 0.11$	0.746	
Education	$F_{(1,25)} = 0.56$	0.462	
Response frequency			
Condition (distance, natural, and indulge)	$F_{(1.16,29.0)} = 0.02$	0.912[a]	
Group × condition	$F_{(1.16,29.0)} = 0.03$	0.895[a]	
Valuation (0, 1, 2, and 3 €)	$F_{(2.13,53.15)} = 1.30$	0.283[a]	
Group × valuation	$F_{(2.13,53.15)} = 3.89$	0.024[a]	0.13*
Condition × valuation	$F_{(3.44,86.11)} = 0.76$	0.536[a]	
Group × condition × valuation	$F_{(3.44,86.11)} = 1.45$	0.231[a]	
Group	$F_{(1,25)} = 0.27$	0.605	
Age	$F_{(1,25)} = 0.20$	0.655	
Education	$F_{(1,25)} = 0.11$	0.747	

*Statistical significance, [a]Greenhouse-Geisser correction for non-sphericity.

trial condition and group, there were also no statistically significant effects. Nonetheless, we found a main effect of the cognitive regulation condition in the left hemisphere in the superior (Brodmann area 22) and middle temporal gyrus (Brodmann area 21), the rolandic operculum, and the precentral gyrus (Brodmann area 6) [$7.87 \leq F_{(2,54)} \leq 13.97$, $p \leq 0.001$, 99 voxels, Montreal Neurological Institute peak voxel coordinates -60 -6 -4). *Post hoc* paired *t*-tests with Bonferroni correction demonstrated that the distance and indulge trials elicited lower activity than natural trials and that distance trials lead to higher responses than indulge trials in these regions [distance vs. natural $t_{(28)} = 2.97$, $p = 0.018$, $d = 1.12$; distance vs. indulge $t_{(28)} = 2.68$, $p = 0.036$, $d = 1.01$; natural vs. indulge $t_{(28)} = 4.97$, $p = 9 \times 10^{-5}$, $d = 1.88$] (**Figure 5**).

With the models (2) – (4), we tested if food valuation/bidding behavior was associated with different brain activation between groups after each regulation condition, with parametric modulation by bid value (model 2), pre-rating score (model 3), and reaction time (model 4). No statistically significant regions were identified for overall differences between groups during bidding (main effect of group) for the models (2) – (4). Additionally, no statistically significant active regions were found for interaction effects of group and the bids after each category of cognitive regulation (group × cognitive regulation condition), and the main effect of the condition was also not statistically significant for the models (2) – (4).

Task Validity

Given that our fMRI task was adapted from Hutcherson et al. (2012), here we compared our main results with these authors' significant findings to study the task validity. Since we observed behavioral differences between the control and stress groups, we assessed the validity of the task only with the control group.

As observed by Hutcherson et al. (2012), we also saw that the control group took longer while bidding after distance [$t_{(13)} = 4.82$, $p = 0.001$, $d = 2.67$, with Bonferroni correction] and indulge trials [$t_{(13)} = 3.07$, $p = 0.027$, $d = 1.70$, with Bonferroni correction] than natural trials [group × condition $F_{(1.42,18.43)} = 7.06$, $p = 0.010$, $\chi^2 = 0.35$, Greenhouse-Geisser correction for non-sphericity] (**Figure 2**). Moreover, the distance trials were also associated with the longest reaction time (778.30 ± 198.70 ms), followed by indulge (744.38 ± 125.21 ms),

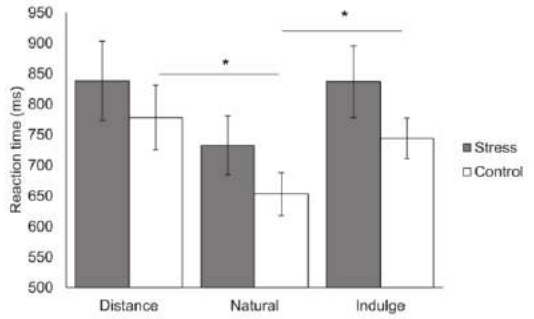


FIGURE 2 | Representation of the reaction time for the different regulation conditions (natural, distance, and indulge) for the stress and control group. The reaction time for natural trials was shorter than for distance [$t_{(13)} = 4.82$, $p = 0.001$, $d = 2.67$] and indulge trials [$t_{(13)} = 3.07$, $p = 0.027$, $d = 1.70$] in the control group but no statistically significant differences occurred in the stress group. The black star represents statistically significant differences. The main bars represent the mean values and the error bars represent the standard error.

and natural (652.98 ± 131.97 ms) trials. These reaction times values are consistent with the previous study.

Concerning the bid value, similarly to Hutcherson et al. (2012), we observed a main effect of the cognitive regulation condition (distance, natural, and indulge) in controls [$F_{(1.23,16.05)} = 16.88$, $p = 4.650 \times 10^{-4}$, $\chi^2 = 0.56$, Greenhouse-Geisser correction for non-sphericity]. The control participants bided higher on indulge [1.74 ± 0.43 €; $t_{(13)} = 2.89$, $p = 0.038$, $d = 1.60$, with Bonferroni correction] and lower on distance [1.04 ± 0.28 €; $t_{(13)} = 4.22$, $p = 0.003$, $d = 2.34$, with Bonferroni correction] compared to natural trials (1.50 ± 0.23 €). Bids after distance and indulge trials were also statistically significantly different [$t_{(13)} = 4.22$, $p = 0.003$, $d = 2.34$, with Bonferroni correction] (**Figure 3**). The bid values in our study (0, 1, 2, and 3 €) were distinct from the original study ($ 0.0, 0.5, 1.0, 1.5, 2.0, and 2.5), thus we could not compare the average bid values after each condition trial.

For neuroimaging data, we computed the contrasts among the cognitive regulation trials in the control group to compare our results with the original study: Distance > Natural, Natural > Distance, Indulge > Natural, Natural > Indulge, Distance > Indulge, and Indulge > Distance. We applied cluster correction for multiple comparisons (90 voxels as described in the section "Materials and Methods"). We found statistically significant results only for the contrasts Distance > Natural and Indulge > Natural. These results are in agreement with Hutcherson et al. (2012)'s findings if the same minimum cluster size is considered. For the contrast Distance > Natural, similarly to the original work, we also found statistically significant activation in temporal and posterior parietal regions (**Supplementary Table S1**). However, results did not show statistically significant activity in medial and ventrolateral prefrontal regions. For the contrast Indulge > Natural, we found statistically significant responses in the anterior cingulate cortex, the ventral, medial, and superior prefrontal cortex, temporal and parietal regions, and the supplementary motor area (**Supplementary Table S1**). Thus, our results are concordant with these authors' previous findings.

DISCUSSION

We studied how chronic stress influences decision-making on food valuation after cognitive regulation (increasing/indulge or decreasing/distance food craving) in medical students. Behavioral, biochemical and neuroimaging analysis were performed to address this question. We found that stressed participants present decreased food valuation scores. This result was reinforced by a higher number of responses for the lowest bid values for food in the stress group. The biochemical analysis (serum levels of insulin, cortisol, and glucose) did not show statistically significant differences between the control and stress group. The neuroimaging results did not demonstrate statistically significant differently activated brain regions between the stressed and control participants during cognitive regulation of craving and decision-making/bidding.

Although the acute stress response is generally beneficial, i.e., promotes adaptation to stressful stimulus, prolonged activation of the stress response produces deleterious effects on the body and brain, affecting cognitive processes such as decision-making (Mcewen, 2004; McEwen and Gianaros, 2011; Sousa, 2016). One of the main findings of the present study is that stressed individuals presented lower scores during food valuation, in contrast with our initial hypothesis. This may translate a blunted hedonic capacity or reward sensitivity (Berenbaum and Connelly, 1993; Porcelli et al., 2012; Bryce and Floresco, 2016; Porcelli and Delgado, 2017; Uy and Galván, 2017), as anhedonia has been associated with higher perceived stress scale scores (Pizzagalli et al., 2007) and stress causes changes in regions related to hedonic/rewarding behavior such as the amygdala, orbitofrontal cortex, vmPFC, and ventral and dorsal striatum (Gorwood, 2008; Porcelli et al., 2012; Bessa et al., 2013; Stark et al., 2015). Moreover, the distribution of the number of responses was higher for lower bids in the stress group, i.e., stressed subjects seemed less prone to place high bids for food. A previous work including a food-related task discovered decreased reward sensitivity associated with alterations in the putamen activity after acute stress induction (Born et al., 2010). Another report pointed out that acute stress does not potentiate craving after stimulation with food pictures (Stojek et al., 2015). Moreover, animal research indicates that acute stress reduces the motivation to work for food rewards (Bryce and Floresco, 2016). Other studies have also shown that acute and chronic stress mitigate brain responses to food stimuli in reward pathways (Wierenga et al., 2018). These results support the idea that stress participants have a reduced valuation attributed to food rewards. However, other studies have shown increased sensitivity to high-caloric food rewards in stressed individuals (Razzoli et al., 2017; Ans et al., 2018; Berg Schmidt et al., 2018; Ferrer-Cascales et al., 2018). Reward processing might be different when participants are stimulated with food pictures or real food. Moreover, the inclusion of chronic or acute stress

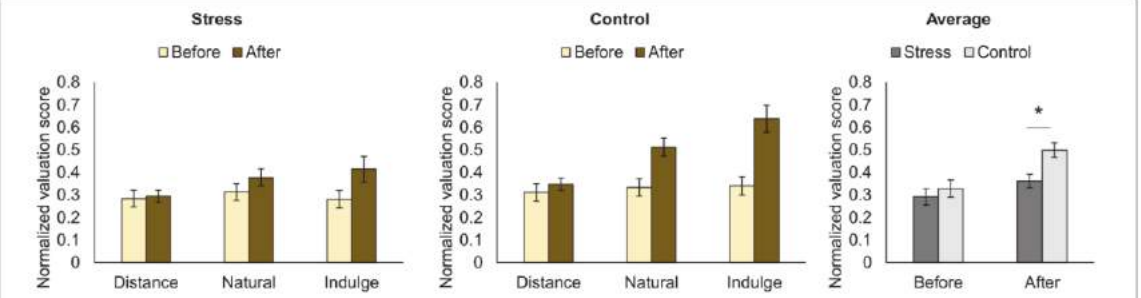


FIGURE 3 | Representation of the normalized rating scores for food pictures for each trial condition (natural, distance, and indulge) before performing the functional magnetic resonance task (before cognitive regulation) and during the functional magnetic resonance task (after cognitive regulation) for the stress and control groups (the normalized scores represent the ratio between given score and maximum score). Before cognitive regulation, we did not find statistically significant differences between groups or within group in terms of food valuation across the conditions. After cognitive regulation, the stress group had lower average valuation scores in comparison to the control group [group $F_{(1,25)} = 6.91$, $p = 0.014$, $\chi^2 = 0.22$]. The black star represents statistically significant differences. The main bars represent the mean values and the error bars represent the standard error.

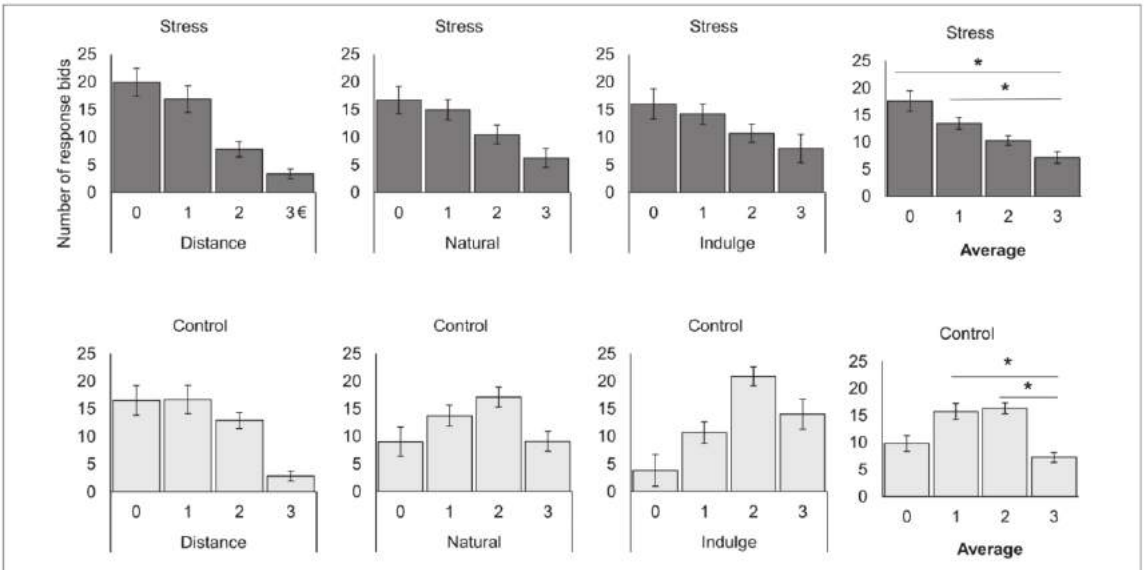


FIGURE 4 | Representation of the number of responses for the stress and control groups during bidding for each cognitive regulation trial and for the average of all trials. On average, the stress participants bided more often 0 [$t_{(14)} = 3.93$, $p = 0.009$, $d = 1.78$] and 1 € [$t_{(14)} = 3.38$, $p = 0.027$, $d = 1.81$] than 3 €, while control subjects bided more times 1 [$t_{(13)} = 3.94$, $p = 0.010$, $d = 2.18$] and 2 € [$t_{(13)} = 5.91$, $p = 3.090 \times 10^{-4}$, $d = 3.28$] than 3 €. The black star represents statistically significant differences. The main bars represent the mean values and the error bars represent the standard error.

models might also account for different results regarding reward sensitivity (Porcelli and Delgado, 2017). However, our results need confirmation with larger sample sizes.

While bidding, the stressed subjects did not present differential brain activity when compared to control subjects, despite the behavioral differences in the valuation score. We were expecting that poor cognitive self-control reflected in reduced prefrontal activation (Hare et al., 2009, 2011; Kober et al., 2010; Hutcherson et al., 2012) would lead to higher responses in striatal and amygdalar regions associated with increased reward sensitivity (Louis et al., 2009; Tryon et al., 2013; Maier et al., 2015; Neseliler et al., 2017). Other studies have found controversial results demonstrating that reduced striatal activity was associated with high levels of stress and increased food craving (Hommer et al., 2013). However, we did not observe cognitive differences between the groups and reward sensitivity was decreased. Our sample size may have limited the statistical power of this analysis. Thus, further research should be conducted to understand the neural correlates of decision-making after cognitive regulation since our results are not conclusive.

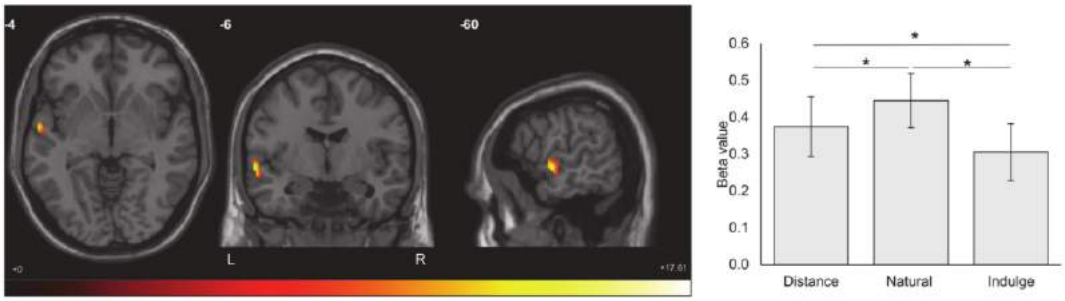


FIGURE 5 | Statistically significant brain regions resulting from the main effect of the cognitive regulation condition (natural, indulge, and distance) for both groups (cluster correction for multiple comparisons, minimum voxel size of 90, $p < 0.001$, $F_{(2,54)}$ value between 7.87 and 13.97 represented by the colored bar). The distance and indulge trials elicited lower activity than natural trials, and the distance trials lead to higher responses than indulge trials in these regions (distance vs. natural $t_{(28)} = 2.97$, $p = 0.018$, $d = 1.12$; distance vs. indulge $t_{(28)} = 2.68$, $p = 0.036$, $d = 1.01$; natural vs. indulge $t_{(28)} = 4.97$, $p = 9 \times 10^{-5}$, $d = 1.88$). These regions include the superior (Brodmann area 22) and middle temporal gyrus (Brodmann area 21), the rolandic operculum, and the precentral gyrus (Brodmann area 6). The numbers above the slices represent the Montreal Neurological Institute peak voxel coordinates. The black star represents statistically significant differences. The main bars represent the mean values and the error bars represent the standard error. L, left; R, Right.

Our neuroimaging results did not show brain activity differences between groups during cognitive regulation. According to previous studies, the vmPFC and dlPFC are regions responsible for cognitive regulation in this decision-making context (Hare et al., 2009, 2011; Kober et al., 2010; Hutcherson et al., 2012). Thus, the absence of changes in these regions between groups in our work might indicate that the processes for cognitive regulation of food craving are not affected by chronic stress, or that our specific model of chronic stress might not lead to changes in cognitive modulation of craving. However, previous works revealed that cognitive control is diminished under stress, leading to emotional and habitual-biased decision-making (Yu, 2016), and increased reward sensitivity for food (Tryon et al., 2013; Maier et al., 2015; Neseliler et al., 2017). Our moderate sample size might have hindered putative differences between groups. Nonetheless, as shown in **Figures 2, 3**, stressed participants were able to modulate their responses, demonstrating an effective cognitive regulation, although the average food bidding score was lower than in controls. Both groups were capable of effectively using cognitive regulation to change the value placed on food during regulated trials. Moreover, both groups took longer times during bidding after regulated trials. Indeed, we found that activity in the superior and middle temporal gyrus, rolandic operculum, and precentral gyrus was differently modulated by trials with cognitive regulation of craving versus non-regulated trials in both groups. Previous authors provided evidence for a functional connection between the vmPFC and the precentral gyrus during food-related decisions, and for the correlation between food ratings and the response in the middle temporal gyrus (Kober et al., 2010; Hare et al., 2011; Hutcherson et al., 2012). Moreover, the temporal gyrus is also involved in food imagery (Hommer et al., 2013). Thus, the regulatory success does not seem to be affected by stress. During cognitive control tasks, attentional narrowing might occur after stimulation with negative pictures with threat and sadness-related content (van Steenbergen et al., 2011; Melcher et al., 2012; Papazacharias et al., 2015). Thus, the negative emotional state in the stress group (e.g., fear of falling the final exam) might have led to higher attentional focus during cognitive regulation that might compensate cognitive deficits associated with chronic stress. Nonetheless, our results need further validation with larger sample sizes to rule out a putative effect of chronic stress in cognitive regulation of craving.

Insulin, cortisol, and glucose levels are expected to decrease after fasting (Kirschbaum et al., 1997; Adam and Epel, 2007; Figlewicz, 2015; Tiedemann et al., 2017). However, peripheral concentrations of cortisol rise after stimulation with food images due to appetite enhancement, while insulin and glucose levels seem to be unaffected (Schmid et al., 2005; Schüssler et al., 2012; Kroemer et al., 2013). In our study, both groups presented a decreased in insulin, glucose, and cortisol levels after the fMRI task. Thus, the effects of fasting might have potentially surpassed the effects of stimulation with food pictures (Brede et al., 2017). Nonetheless, this hypothesis needs further testing. We were expecting increased craving in the stress group after a deficient cognitive regulation and increased reward sensitivity to food (Tryon et al., 2013; Maier et al., 2015; Neseliler et al., 2017). However, our results agree with the fact that we found reduced valuation of rewards in the absence of cognitive regulation alterations in the stress group, suggesting that overall craving was reduced. For controls, the instructions to differently modulate craving might have led to balanced changes in blood parameters after stimulation with food pictures. Thus, our results might derive from fasting since they occurred in both groups.

Importantly, our results are limited by the sample size. These results need to be replicated with larger samples to avoid false negative and positive conclusions. Moreover, the results might have been influenced by the unbalanced proportion of females and males per group, given that gender differences were found in decision-making under stress (Yu, 2016; Wemm and Wulfert, 2017). However, we focused on group differences and groups were matched for gender ratio.

Our results show that the capacity to perform cognitive regulation of craving is not impaired after prolonged stress. However, chronic stress reduces the value attributed to food rewards after craving modulation. Importantly, our conclusions are limited by the small sample size and need further validation with larger samples. These findings are relevant to guide subsequent studies on cognitive regulation of food-related decision-making for eating and obesity-associated disorders. Cognitive control techniques might be used to tackle decision-making impairments in these conditions (Louis et al., 2009; May et al., 2012).

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the Declaration of Helsinki. All subjects gave written informed consent. The protocol was approved by the Ethics Subcommittee for the Life and Health Sciences of University of Minho, Portugal, and by the Ethics Committee of the Hospital of Braga, Portugal.

AUTHOR CONTRIBUTIONS

SF, CV, PM, RM, AC, PMore, and CP-N acquired, analyzed, and interpreted the data and wrote the manuscript. NS and PMorg supervised the work, interpreted the data, and wrote and reviewed the manuscript. All authors participated in the design of the experiments and approved the manuscript.

FUNDING

This work was funded by the MyHealth project (DoIT – Desenvolvimento e Operacionalização da Investigação de Translação, Contract DoIT-13853) and the BIAL Foundation, Porto, Portugal (Grant No. PT/FB/BL-2016-206). This work was also funded by the FEDER funds, through the Competitiveness Factors Operational Programme (COMPETE), and by national funds, through the Foundation for Science and Technology (FCT), under the scope of the project POCI-01-0145-FEDER-007038. This manuscript has been developed under the scope of the project NORTE-01-0145-FEDER-000013, supported by the Northern Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020 Partnership Agreement, through the European Regional Development Fund (FEDER). PaM was supported by a fellowship of the project "SwitchBox" (Contract HEALTH-F2-2010-259772). SF was supported by a combined Ph.D. scholarship from the FCT and the company iCognitus4ALL – IT Solutions, Lda (PD/BDE/127839/2016). RM was supported by the combined FCT and Enlightenment, Lda fellowship (PDE/BDE/113604/2015) from the PhDiHES program.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2019.00724/full#supplementary-material

REFERENCES

Adam, T. C., and Epel, E. S. (2007). Stress, eating and the reward system. *Physiol. Behav.* 91, 449–458. doi: 10.1016/j.physbeh.2007.04.011

Ans, A. H., Anjum, I., Satija, V., Inayat, A., Asghar, Z., Akram, I., et al. (2018). Neurohormonal regulation of appetite and its relationship with stress: a mini literature review. *Cureus* 10:e3032. doi: 10.7759/cureus.3032

Arnsten, A. F. T. (2015). Stress weakens prefrontal networks: molecular insults to higher cognition. *Nat. Neurosci.* 18, 1376–1385. doi: 10.1038/nn.4087

Balleine, B. (2005). Neural bases of food-seeking: affect, arousal and reward in corticostriatolimbic circuits?. *Physiol. Behav.* 86, 717–730. doi: 10.1016/j.physbeh.2005.08.061

Basten, U., Biele, G., Heekeren, H. R., and Fiebach, C. J. (2010). How the brain integrates costs and benefits during decision making. *Proc. Natl. Acad. Sci. U.S.A.* 107, 21767–21772. doi: 10.1073/pnas.0908104107

Beck, A. T., Epstein, N., Brown, G., and Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *J. Consult. Clin. Psychol.* 56, 893–897. doi: 10.1037/0022-006X.56.6.893

Beck, A. T., Steer, R. A., Ball, R., and Ranieri, W. (1996). Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J. Pers. Assess.* 67, 588–597. doi: 10.1207/s15327752jpa6703_13

Becker, G. M., Degroot, M. H., and Marschak, J. (1964). Measuring utility by a single-response sequential method. *Behav. Sci.* 9, 226–232. doi: 10.1002/bs.3830090304

Berenbaum, H., and Connelly, J. (1993). The effect of stress on hedonic capacity. *J. Abnorm. Psychol.* 102, 474–481. doi: 10.1037/0021-843X.102.3.474

Berg Schmidt, J., Johanneson Bertolt, C., Sjödin, A., Ackermann, F., Vibeke Schmedes, A., Lynge Thomsen, H., et al. (2018). Does stress affect food preferences? – a randomized controlled trial investigating the effect of examination stress on measures of food preferences and obesogenic behavior. *Stress* 21, 556–563. doi: 10.1080/10253890.2018.1494149

Bessa, J. M., Morais, M., Marques, F., Pinto, L., Palha, J. A., Almeida, O. F. X., et al. (2013). Stress-induced anhedonia is associated with hypertrophy of medium spiny neurons of the nucleus accumbens. *Transl. Psychiatry* 3, e266–e266. doi: 10.1038/tp.2013.39

Born, J. M., Lemmens, S. G. T., Rutters, F., Nieuwenhuizen, A. G., Formisano, E., Goebel, R., et al. (2010). Acute stress and food-related reward activation in the brain during food choice during eating in the absence of hunger. *Int. J. Obes.* 34, 172–181. doi: 10.1038/ijo.2009.221

Brede, S., Sputh, A., Hartmann, A.-C., Hallschmid, M., Lehnert, H., and Klement, J. (2017). Visual food cues decrease postprandial glucose concentrations in lean and obese men without affecting food intake and related endocrine parameters. *Appetite* 117, 255–262. doi: 10.1016/j.appet.2017.07.001

Bryce, C. A., and Floresco, S. B. (2016). Perturbations in effort-related decision-making driven by acute stress and corticotropin-releasing factor. *Neuropsychopharmacology* 41, 2147–2159. doi: 10.1038/npp.2016.15

Chen, Y., and Baram, T. Z. (2016). Toward understanding how early-life stress reprograms cognitive and emotional brain networks. *Neuropsychopharmacology* 41, 197–206. doi: 10.1038/npp.2015.181

Christopoulos, G. I., Tobler, P. N., Bossaerts, P., Dolan, R. J., and Schultz, W. (2009). Neural correlates of value, risk, and risk aversion contributing to decision making under risk. *J. Neurosci.* 29, 12574–12583. doi: 10.1523/JNEUROSCI.2614-09.2009

Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *J. Health Soc. Behav.* 24:385. doi: 10.2307/2136404

Delgado, M. R., Gillis, M. M., and Phelps, E. A. (2008). Regulating the expectation of reward via cognitive strategies. *Nat. Neurosci.* 11, 880–881. doi: 10.1038/nn.2141

Dias-Ferreira, E., Sousa, J. C., Melo, I., Morgado, P., Mesquita, A. R., Cerqueira, J. J., et al. (2009). Chronic stress causes frontostriatal reorganization and affects decision-making. *Science* 325, 621–625. doi: 10.1126/science.1171203

Fehr, E., and Camerer, C. F. (2007). Social neuroeconomics: the neural circuitry of social preferences. *Trends Cogn. Sci.* 11, 419–427. doi: 10.1016/j.tics.2007.09.002

Ferrer-Cascales, R., Albaladejo-Blázquez, N., Ruiz-Robledillo, N., Rubio-Aparicio, M., Laguna-Pérez, A., and Zaragoza-Martí, A. (2018). Low adherence to the mediterranean diet in isolated adolescents: the mediation effects of stress. *Nutrients* 10:1894. doi: 10.3390/nu10121894

Figlewicz, D. P. (2015). Modulation of food reward by endocrine and environmental factors. *Psychosom. Med.* 77, 664–670. doi: 10.1097/PSY.0000000000000146

Gold, J. I., and Shadlen, M. N. (2007). The neural basis of decision making. *Annu. Rev. Neurosci.* 30, 535–574. doi: 10.1146/annurev.neuro.29.051605.113038

Gorwood, P. (2008). Neurobiological mechanisms of anhedonia. *Dialogues Clin. Neurosci.* 10, 291–299.

Hare, T. A., Camerer, C. F., and Rangel, A. (2009). Self-control in decision-making involves modulation of the vmpfc valuation system. *Science* 324, 646–648. doi: 10.1126/science.1168450

Hare, T. A., Malmaud, J., and Rangel, A. (2011). Focusing attention on the health aspects of foods changes value signals in vmpfc and improves dietary choice. *J. Neurosci.* 31, 11077–11087. doi: 10.1523/JNEUROSCI.6383-10.2011

Hommer, R. E., Seo, D., Lacadie, C. M., Chaplin, T. M., Mayes, L. C., Sinha, R., et al. (2013). Neural correlates of stress and favorite-food cue exposure in adolescents: a functional magnetic resonance imaging study. *Hum. Brain Mapp.* 34, 2561–2573. doi: 10.1002/hbm.22089

Hutcherson, C. A., Plassmann, H., Gross, J. J., and Rangel, A. (2012). Cognitive regulation during decision making shifts behavioral control between ventromedial and dorsolateral prefrontal value systems. *J. Neurosci.* 32, 13543–13554. doi: 10.1523/JNEUROSCI.6387-11.2012

Kirschbaum, C., Bono, E. G., Rohleder, N., Gessner, C., Pirke, K. M., Salvador, A., et al. (1997). Effects of fasting and glucose load on free cortisol responses to stress and nicotine. *J. Clin. Endocrinol. Metab.* 82, 1101–1105. doi: 10.1210/jcem.82.4.3882

Kober, H., Mende-Siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., et al. (2010). Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc. Natl. Acad. Sci. U.S.A.* 107, 14811–14816. doi: 10.1073/pnas.1007779107

Kroemer, N. B., Krebs, L., Kobiella, A., Grimm, O., Vollstädt-Klein, S., Wolfensteller, U., et al. (2013). (Still) longing for food: insulin reactivity modulates response to food pictures. *Hum. Brain Mapp.* 34, 2367–2380. doi: 10.1002/hbm.22071

Louis, W. R., Chan, M. K.-H., and Greenbaum, S. (2009). Stress and the theory of planned behavior: understanding healthy and unhealthy eating intentions. *J. Appl. Soc. Psychol.* 39, 472–493. doi: 10.1111/j.1559-1816.2008.00447.x

Magalhães, R., Barrière, D. A., Novais, A., Marques, F., Marques, P., Cerqueira, J., et al. (2018). The dynamics of stress: a longitudinal MRI study of rat brain structure and connectome. *Mol. Psychiatry* 23, 1998–2006. doi: 10.1038/mp.2017.244

Maier, S. U., Makwana, A. B., and Hare, T. A. (2015). Acute stress impairs self-control in goal-directed choice by altering multiple functional connections within the brain's decision circuits. *Neuron* 87, 621–631. doi: 10.1016/j.neuron.2015.07.005

May, J., Andrade, J., Kavanagh, D. J., and Hetherington, M. (2012). Elaborated intrusion theory: a cognitive-emotional theory of food craving. *Curr. Obes. Rep.* 1, 114–121. doi: 10.1007/s13679-012-0010-12

Mcewen, B. S. (2004). Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann. N. Y. Acad. Sci.* 1032, 1–7. doi: 10.1196/annals.1314.001

McEwen, B. S., and Gianaros, P. J. (2011). Stress- and allostasis-induced brain plasticity. *Annu. Rev. Med.* 62, 431–445. doi: 10.1146/annurev-med-052209-100430

McGuire, J. T., and Kable, J. W. (2012). Decision makers calibrate behavioral persistence on the basis of time-interval experience. *Cognition* 124, 216–226. doi: 10.1016/j.cognition.2012.03.008

Melcher, T., Obst, K., Mann, A., Paulus, C., and Gruber, O. (2012). Antagonistic modulatory influences of negative affect on cognitive control: Reduced and enhanced interference resolution capability after the induction of fear and sadness. *Acta Psychol.* 139, 507–514. doi: 10.1016/j.actpsy.2012.01.012

Minkley, N., and Kirchner, W. H. (2012). Influence of test tasks with different cognitive demands on salivary cortisol concentrations in school students. *Int. J. Psychophysiol.* 86, 245–250. doi: 10.1016/j.ijpsycho.2012.09.015

Morgado, P., Freitas, D., Bessa, J. M., Sousa, N., and Cerqueira, J. J. (2013). Perceived stress in obsessive–compulsive disorder is related with obsessive but not compulsive symptoms. *Front. Psychiatry* 4:21. doi: 10.3389/fpsyt.2013.00021

Morgado, P., Marques, F., Ribeiro, B., Leite-Almeida, H., Pêgo, J. M., Rodrigues, A. J., et al. (2015a). Stress induced risk-aversion is reverted by D2/D3 agonist in the rat. *Eur. Neuropsychopharmacol.* 25, 1744–1752. doi: 10.1016/j.euroneuro.2015.07.003

Morgado, P., Sousa, N., and Cerqueira, J. J. (2015b). The impact of stress in decision making in the context of uncertainty. *J. Neurosci. Res.* 93, 839–847. doi: 10.1002/jnr.23521

Morgado, P., Silva, M., Sousa, N., and Cerqueira, J. J. (2012). Stress transiently affects pavlovian-to-instrumental transfer. *Front. Neurosci.* 6:93. doi: 10.3389/fnins.2012.00093

Neseliler, S., Tannenbaum, B., Zacchia, M., Larcher, K., Coulter, K., Lamarche, M., et al. (2017). Academic stress and personality interact to increase the neural response to high-calorie food cues. *Appetite* 116, 306–314. doi: 10.1016/j.appet.2017.05.016

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D. E., et al. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage* 23, 483–499. doi: 10.1016/j.neuroimage.2004.06.030

Papazacharias, A., Taurisano, P., Fazio, L., Gelao, B., Di Giorgio, A., Lo Bianco, L., et al. (2015). Aversive emotional interference impacts behavior and prefronto-striatal activity during increasing attentional control. *Front. Behav. Neurosci.* 9:97. doi: 10.3389/fnbeh.2015.00097

Phillips, M. L., Drevets, W. C., Rauch, S. L., and Lane, R. (2003). Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biol. Psychiatry* 54, 515–528. doi: 10.1016/S0006-3223(03)00171-179

Pizzagalli, D. A., Bogdan, R., Ratner, K. G., and Jahn, A. L. (2007). Increased perceived stress is associated with blunted hedonic capacity: Potential implications for depression research. *Behav. Res. Ther.* 45, 2742–2753. doi: 10.1016/j.brat.2007.07.013

Plassmann, H., O'Doherty, J., and Rangel, A. (2007). Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. *J. Neurosci.* 27, 9984–9988. doi: 10.1523/JNEUROSCI.2131-07.2007

Platt, M. L., and Huettel, S. A. (2008). Risky business: the neuroeconomics of decision making under uncertainty. *Nat. Neurosci.* 11, 398–403. doi: 10.1038/nn2062

Porcelli, A. J., and Delgado, M. R. (2017). Stress and decision making: effects on valuation, learning, and risk-taking. *Curr. Opin. Behav. Sci.* 14, 33–39. doi: 10.1016/j.cobeha.2016.11.015

Porcelli, A. J., Lewis, A. H., and Delgado, M. R. (2012). Acute stress influences neural circuits of reward processing. *Front. Neurosci.* 6:157. doi: 10.3389/fnins.2012.00157

Rangel, A., Camerer, C., and Montague, P. R. (2008). A framework for studying the neurobiology of value-based decision making. *Nat. Rev. Neurosci.* 9, 545–556. doi: 10.1038/nrn2357

Razzoli, M., Pearson, C., Crow, S., and Bartolomucci, A. (2017). Stress, overeating, and obesity: insights from human studies and preclinical models. *Neurosci. Biobehav. Rev.* 76, 154–162. doi: 10.1016/j.neubiorev.2017.01.026

Sandi, C. (2013). Stress and cognition. *Wiley Interdiscip. Rev. Cogn. Sci.* 4, 245–261. doi: 10.1002/wcs.1222

Schmid, D. A., Held, K., Ising, M., Uhr, M., Weikel, J. C., and Steiger, A. (2005). Ghrelin stimulates appetite, imagination of food, gh, acth, and cortisol, but does not affect leptin in normal controls. *Neuropsychopharmacology* 30, 1187–1192. doi: 10.1038/sj.npp.1300670

Schüssler, P., Kluge, M., Yassouridis, A., Dresler, M., Uhr, M., and Steiger, A. (2012). Ghrelin levels increase after pictures showing food. *Obesity* 20, 1212–1217. doi: 10.1038/oby.2011.385

Soares, J. M., Sampaio, A., Ferreira, L. M., Santos, N. C., Marques, F., Palha, J. A., et al. (2012). Stress-induced changes in human decision-making are reversible. *Transl. Psychiatry* 2, e131–e131. doi: 10.1038/tp.2012.59

Sousa, N. (2016). The dynamics of the stress neuromatrix. *Mol. Psychiatry* 21, 302–312. doi: 10.1038/mp.2015.196

Starcke, K., and Brand, M. (2012). Decision making under stress: A selective review. *Neurosci. Biobehav. Rev.* 36, 1228–1248. doi: 10.1016/j.neubiorev.2012.02.003

Stark, E. A., Parsons, C. E., Van Hartevelt, T. J., Charquero-Ballester, M., McManners, H., Ehlers, A., et al. (2015). Post-traumatic stress influences the brain even in the absence of symptoms: a systematic, quantitative meta-analysis of neuroimaging studies. *Neurosci. Biobehav. Rev.* 56, 207–221. doi: 10.1016/j.neubiorev.2015.07.007

Stojek, M. K., Fischer, S., and MacKillop, J. (2015). Stress, cues, and eating behavior. Using drug addiction paradigms to understand motivation for food. *Appetite* 92, 252–260. doi: 10.1016/j.appet.2015.05.027

Tiedemann, L. J., Schmid, S. M., Hettel, J., Giesen, K., Francke, P., Büchel, C., et al. (2017). Central insulin modulates food valuation via mesolimbic pathways. *Nat. Commun.* 8:16052. doi: 10.1038/ncomms16052

Tryon, M. S., Carter, C. S., DeCant, R., and Laugero, K. D. (2013). Chronic stress exposure may affect the brain's response to high calorie food cues and predispose to obesogenic eating habits. *Physiol. Behav.* 120, 233–242. doi: 10.1016/j.physbeh.2013.08.010

Uy, J. P., and Galván, A. (2017). Acute stress increases risky decisions and dampens prefrontal activation among adolescent boys. *Neuroimage* 146, 679–689. doi: 10.1016/j.neuroimage.2016.08.067

van Steenbergen, H., Band, G. P. H., and Hommel, B. (2011). Threat but not arousal narrows attention: evidence from pupil dilation and saccade control. *Front. Psychol.* 2:281. doi: 10.3389/fpsyg.2011.00281

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., and Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 59, 1037–1050. doi: 10.1016/j.neuron.2008.09.006

Wemm, S. E., and Wulfert, E. (2017). Effects of acute stress on decision making. *Appl. Psychophysiol. Biofeedback* 42, 1–12. doi: 10.1007/s10484-016-9347-9348

Wierenga, C. E., Lavender, J. M., and Hays, C. C. (2018). The potential of calibrated fMRI in the understanding of stress in eating disorders. *Neurobiol. Stress* 9, 64–73. doi: 10.1016/j.ynstr.2018.08.006

Yu, R. (2016). Stress potentiates decision biases: A stress induced deliberation-to-intuition (SIDI) model. *Neurobiol. Stress* 3, 83–95. doi: 10.1016/j.ynstr.2015.12.006

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Ferreira, Veiga, Moreira, Magalhães, Coelho, Marques, Portugal-Nunes, Sousa and Morgado. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Neuroscience

CORRECTION
published: 22 November 2019
doi: 10.3389/fnins.2019.01252

Corrigendum: Reduced Hedonic Valuation of Rewards and Unaffected Cognitive Regulation in Chronic Stress

Sónia Ferreira[1,2†], *Carlos Veiga*[1,2†], *Pedro Moreira*[1,2], *Ricardo Magalhães*[1,2], *Ana Coelho*[1,2], *Paulo Marques*[1,2], *Carlos Portugal-Nunes*[1,2], *Nuno Sousa*[1,2,3] *and Pedro Morgado*[1,2,3*]

[1] *Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal,* [2] *ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal,* [3] *Clinical Academic Center – Braga, Braga, Portugal*

Keywords: stress, decision-making, cognition, magnetic resonance imaging, fMRI, reward, human, food

A Corrigendum on

Reduced Hedonic Valuation of Rewards and Unaffected Cognitive Regulation in Chronic Stress
by Ferreira, S., Veiga, C., Moreira, P., Magalhães, R., Coelho, A., Marques, P., et al. (2019). Front. Neurosci. 13:724. doi: 10.3389/fnins.2019.00724

OPEN ACCESS

Approved by:
Frontiers Editorial Office, Frontiers Media SA, Switzerland

***Correspondence:**
Pedro Morgado
pedromorgado@med.uminho.pt

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Decision Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *04 November 2019*
Accepted: *05 November 2019*
Published: *22 November 2019*

Citation:
Ferreira S, Veiga C, Moreira P, Magalhães R, Coelho A, Marques P, Portugal-Nunes C, Sousa N and Morgado P (2019) Corrigendum: Reduced Hedonic Valuation of Rewards and Unaffected Cognitive Regulation in Chronic Stress. Front. Neurosci. 13:1252. doi: 10.3389/fnins.2019.01252

In the original article, there was an error. The psychometric scale used to measure the depression scores was the "Beck Depression Inventory" and not the "Beck Depression Inventory II."

A correction has been made to the **Materials and Methods**, subsection **Sociodemographic and Psychological Scales**:

"Subjects filled a questionnaire to characterize gender, age, educational level, handedness, and ethnic origin. Weight and height were also measured to prevent the inclusion of participants with an unhealthy body mass index. Subjects were assessed with the 10-items Perceived Stress Scale (PSS-10) (Cohen et al., 1983; Morgado et al., 2013), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), and the Beck Depression Inventory (BDI) (Beck et al., 1996). PSS-10 measures the extent to which participants perceived their life as unpredictable, uncontrollable, and overloaded during the previous month. The higher the score, the greater the intensity of perceived stress. BAI measures the severity of an individual's anxiety during the previous week. Scores lower than 8 indicate minimal anxiety. Scores higher than 7, 15, and 25 indicate mild, moderate, and severe anxiety, respectively. BDI measures the severity of depression and can be used as a screening tool. Scores lower than 14 indicate minimal depression. Higher scores indicate more severe depressive symptoms."

A correction has also been made to **Results**, subsection **Psychological Assessment**:

"The stress group revealed higher levels of perceived stress (mean ± standard deviation 15.07 ± 5.23) than the control group (8.64 ± 5.27) as assessed by PSS-10 [$t_{(27)} = 3.30$, $p = 0.003$, effect size $d = 1.27$]. No statistically significant differences were found for BAI ($U = 117.50$, $p = 0.591$) and BDI ($U = 134.00$, $p = 0.217$) between groups."

Lastly, a correction has been made to the **Abbreviations** section:

"ACTH, adrenocorticotropic hormone; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; dlPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; GLM, general linear model; MNI, Montreal Neurological Institute; PSS-10, 10-items Perceived Stress Scale; vmPFC, ventromedial prefrontal cortex."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

REFERENCES

Beck, A. T., Epstein, N., Brown, G., and Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *J. Consult. Clin. Psychol.* 56, 893–897. doi: 10.1037/0022-006X.56.6.893

Beck, A. T., Steer, R. A., Ball, R., and Ranieri, W. (1996). Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J. Pers. Assess.* 67, 588–597. doi: 10.1207/s15327752jpa6703_13

Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *J. Health Soc. Behav.* 24:385. doi: 10.2307/2136404

Morgado, P., Freitas, D., Bessa, J. M., Sousa, N., and Cerqueira, J. J. (2013). Perceived stress in obsessive–compulsive disorder is related with obsessive but not compulsive symptoms. *Front. Psychiatry* 4:21. doi: 10.3389/fpsyt.2013.00021

Copyright © 2019 Ferreira, Veiga, Moreira, Magalhães, Coelho, Marques, Portugal-Nunes, Sousa and Morgado. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

1. Supplementary material

Table S1 Differential brain activity during cognitive regulation trials (distance, natural, and indulge) within the control group ($p < 0.001$; cluster correction with a minimum of 90 voxels).

Brain regions	Cluster size (voxels)	MNI peak voxel coordinates	Peak voxel intensity
Distance > Natural			
L Calcarine; Posterior cingulate (BA 30); Lingual gyrus; Cuneus; Temporal lobe.	90	-18 -64 6	$t_{(54)} = 4.37$
Natural > Distance			
No statistically significant regions.			
Indulge > Natural			
L Fusiform gyrus (BA 37); Lingual gyrus; Parahippocampal gyrus (BA 36); Cerebellum (anterior and posterior lobe).	448	-28 -42 -22	$t_{(54)} = 4.89$
L Superior (BA 22), middle (BA 21), inferior (BA 20), and transverse (BA 41) temporal gyrus; Superior and middle temporal pole (BA 38); Precentral (BA 4 and 6) and postcentral gyrus; Inferior (BA 44 and 47) and middle frontal gyrus (BA 9); Insula/claustrum (BA13); Rolandic operculum; Inferior orbitofrontal; Inferior frontal operculum; Putamen; Fusiform gyrus.	1944	-50 10 -4	$t_{(54)} = 6.14$
L Parahippocampal gyrus (BA 28 and 34); Amygdala; Superior temporal pole; Subcallosal gyrus; Inferior orbitofrontal.	132	-20 4 -20	$t_{(54)} = 4.53$
R Parahippocampal gyrus (BA 28 and 34); Amygdala; Inferior frontal gyrus (BA 47); Subcallosal gyrus; Insula (BA 13); Superior temporal pole; Gyrus rectus; Inferior orbitofrontal.	153	22 8 -20	$t_{(54)} = 4.48$
R, L Anterior, posterior, and middle cingulate; Lingual gyrus; Precuneus; Cuneus; Cerebellum; R Medial and superior frontal gyrus; Supplementary motor area; Calcarine; Parahippocampal gyrus; L Paracentral lobule; Hippocampus.	2512	-8 -40 6	$t_{(54)} = 5.47$
R Superior (BA 22), middle (BA 21), and transverse temporal gyrus; Insula (BA 13); Superior temporal pole (BA 38); Rolandic operculum; Precentral gyrus.	303	64 -8 -2	$t_{(54)} = 5.25$
R Superior (BA 22), middle (BA 21), and transverse temporal gyrus (BA 42).	278	62 -28 4	$t_{(54)} = 4.84$
R, L Medial (BA 9) and superior frontal gyrus; Anterior (BA 24 and 32) and middle cingulate.	408	16 42 48	$t_{(54)} = 5.23$
R Precentral (BA 4) and postcentral gyrus (BA 3); Superior, inferior, and middle frontal gyrus (BA 9).	550	62 -4 36	$t_{(54)} = 4.68$
R, L middle cingulate gyrus (BA 32); Supplementary motor area (BA 8); Medial and superior frontal gyrus.	96	4 20 44	$t_{(54)} = 3.96$
L Precuneus; Parietal lobe (BA 5 and 7); Paracentral lobule.	102	-4 -54 50	$t_{(54)} = 4.17$
L Precentral (BA 4) and postcentral gyrus (BA 1, 2, and 3); Superior parietal lobe (BA 5).	97	-30 -40 66	$t_{(54)} = 4.39$
R Precentral (BA 4) and postcentral gyrus (BA 2 and 3); Parietal lobe; Paracentral lobule; Medial frontal gyrus.	97	24 -34 72	$t_{(54)} = 4.14$
Natural > Indulge			
No statistically significant regions.			
Distance > Indulge			
No statistically significant regions.			
Indulge > Distance			
No statistically significant regions.			

MNI = Montreal Neurologic Institute; L = Left; R = Right; BA = Brodmann Area.

CHAPTER IV

Frontoparietal hyperconnectivity during cognitive regulation in obsessive-compulsive disorder followed by reward valuation inflexibility

Sónia Ferreira, Pedro Moreira, Ricardo Magalhães, Ana Coelho, Paulo Marques, Carlos Portugal-Nunes, Catarina Silva, Nuno Sousa, Pedro Morgado

Manuscript under minor revision

Frontoparietal hyperconnectivity during cognitive regulation in obsessive-compulsive disorder followed by reward valuation inflexibility

Sónia Ferreira[1,2,3], Pedro Moreira[1,2,3], Ricardo Magalhães[1,2,3], Ana Coelho[1,2,3], Paulo Marques[1,2,3], Carlos Portugal-Nunes[1,2,3], Catarina Silva[1,2,3], Nuno Sousa[1,2,3], and Pedro Morgado[1,2,3]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [2]ICVS-3Bs PT Government Associate Laboratory, Braga/Guimarães, Portugal; [3]Clinical Academic Center-Braga (2CA), Braga, Portugal

1. Abstract

Obsessive-compulsive disorder (OCD) is characterized by cognitive deficits and altered reward processing systems. An imbalance between cognitive and reward pathways may explain the lack of control over obsessions followed by rewarding compulsive behaviors. While the processes of emotional cognitive regulation are widely studied in OCD, the mechanisms of cognitive regulation of reward are poorly described. Our goal was to investigate the OCD impact on cognitive regulation of reward at behavioral and neural functioning levels. OCD and control participants performed a functional magnetic resonance imaging task where they cognitively modulated their craving for food pictures under three cognitive regulation conditions: indulge/increase craving, distance/decrease craving, and natural/no regulation of craving. After regulation, the participants gave each picture a monetary value. We found that OCD patients had fixed food valuation scores while the control group modulated these values accordingly to the regulation conditions. Moreover, we observed frontoparietal hyperconnectivity during cognitive regulation. Our results suggest that OCD is characterized by deficits in cognitive regulation of internal states associated with inflexible behavior during reward processing. These findings bring new insights into the nature of compulsive behaviors in OCD.

2. Introduction

Cognitive regulation refers to the adaptive self-regulation of cognitive processes to reach a goal. These cognitive processes may include thoughts, beliefs, emotion/affective, or hedonic (e.g. food and money) information (Nigg, 2017; Sun & Kober, 2020). The mechanisms of cognitive regulation involve automatic brain responses to external sensory stimuli in subcortical regions (amygdala and ventral striatum/ventral tegmental area) and top-down processes to modulate these subcortical responses originating in the anterior cingulate cortex and the ventromedial (vmPFC), ventrolateral, and dorsolateral prefrontal (dlPFC) cortices. The frontoparietal and cingulo-opercular networks are also engaged during cognitive regulation (Amidfar et al., 2019; Brandl et al., 2019; Cocchi et al., 2013; Cutuli, 2014; Langner et al., 2018; Nigg, 2017; Ochsner et al., 2012; Pruessner et al., 2020).

Obsessive-compulsive disorder (OCD) is a severe chronic disorder characterized by recurrent intrusive thoughts (obsessions) and ritualistic actions (compulsions) intended to diminish the anxiety and distress elicited by obsessions (American Psychiatric Association, 2013). This disorder is characterized by impairments in cognitive regulation processes. Past theories suggest an imbalance between brain systems responsible for cognitive regulation and reward processing in OCD. The inhibition of cognitive regions and the activation of reward areas may lead to compulsive behaviors due to a shift from goal-directed to habitual behavior (Banca et al., 2015; Gillan et al., 2011, 2014, 2015; Göttlich et al., 2014; Voon et al., 2015; Xie et al., 2017). Indeed, compulsions allow temporary relief of the anxiety and distress caused by a lack of control over obsessions, functioning as rewards for OCD individuals (Albertella et al., 2020; Dougherty et al., 2018; G. M. Ferreira et al., 2017; Figee et al., 2011; Grassi et al., 2020; Gruner & Pittenger, 2017; Wi Hoon Jung et al., 2013) and leading to a negative reinforcing cycle (Abramovitch, Anholt, et al., 2019).

However, to the best of our knowledge, previous studies have not addressed the mechanisms of cognitive regulation of reward in OCD. The former literature has focused on the cognitive regulation of emotions in OCD (De Wit et al., 2015; Fernández de la Cruz et al., 2013; Fink et al., 2018; Paul et al., 2016; Maria Picó-Pérez et al., 2019; A. L. L. Thorsen et al., 2019; Yazici & Yazici, 2019). These authors reported reduced cognitive reappraisal abilities and increased use of suppression strategies. Additionally, OCD patients activate less frontoparietal network (FPN) regions during cognitive regulation of affective stimuli (De Wit et al., 2015; Koçak et al., 2011; Simon et al., 2014; A. L. L. Thorsen et al., 2019). Moreover, alterations in the amygdala-insula functional connectivity (FC) associated with cognitive reappraisal deficits were observed in OCD patients (De Wit et al., 2015; Maria Picó-Pérez et al., 2019; A.

L. L. Thorsen et al., 2019). Decreased dlPFC and ventrolateral prefrontal response during cognitive reappraisal is also a common finding across other psychiatric disorders (Zilverstand et al., 2017).

Food paradigms have been applied with animal models of OCD to study reward behavior (Adriani et al., 2012; Cinque et al., 2018) and also with humans to understand reward-related neural responses after cognitive regulation (Demos McDermott et al., 2019; J. E. Han et al., 2018; Lopez et al., 2019; Mehl et al., 2019). OCD is characterized by reward processing impairments underlined by abnormal functioning of circuits involving the orbitofrontal, cingulate, and dlPFC, anterior insula, and deeper cortical regions (nucleus accumbens, amygdala, hippocampus, and thalamus) (Abe et al., 2015; Figee et al., 2011; W. H. Jung et al., 2011; Wi Hoon Jung et al., 2013; Koch et al., 2018; Marsh et al., 2015). OCD individuals respond more to negative cues, often avoiding harmful/risky outcomes (W. H. Jung et al., 2011; Kanen et al., 2019; Sip et al., 2018; Stern & Taylor, 2014), and have reduced sensitivity to positive rewards (Xie et al., 2017). Other authors also found that higher compulsivity is associated with increased attentional control to reward-signaling stimuli (Albertella et al., 2019) and that the anticipation of reward might drive compulsive behaviors in OCD (G. M. Ferreira et al., 2017, 2020). The dlPFC and vmPFC are crucial for cognitive regulation of reward, including the craving for hedonic stimulus (Brandl et al., 2019; Hare et al., 2009; Hutcherson et al., 2012; Kober et al., 2010). The vmPFC is involved in the selection of appropriate cognitive strategies and the integration of reward valuation information accordingly to a specific goal. The dlPFC acts in the regulation of the vmPFC during cognitive regulation being responsible for goal maintenance, monitoring, and manipulation, and attentional shifting processes (Amidfar et al., 2019; Brandl et al., 2019; Langner et al., 2018; Ochsner et al., 2012).

In this study, we adopted a food-related task (S. Ferreira, Veiga, et al., 2019; Hutcherson et al., 2012) to investigate the impact of OCD on cognitive regulation of reward at behavioral and neural functioning levels using functional magnetic resonance imaging (fMRI). During this task, the participants need to cognitively regulate their craving (increase/decrease) while being stimulated with a food picture. After cognitive regulation, they valuate the food picture to analyze the effects of craving regulation. Based on past findings, we hypothesize that cognitive regulation deficits in OCD are associated with diminished function in FPN and associated regions, namely the vmPFC and dlPFC. Moreover, we expect abnormal FC during the cognitive regulation task between the vmPFC/dlPFC and regions within the FPN. Given the lack of previous studies analyzing functional connectivity alterations during cognitive regulation in OCD, we cannot assume the direction of FC alterations. Furthermore, we propose that cognitive regulation deficits are associated with impairments in food-related reward processing, namely increased reward sensitivity.

3. Material and Methods

a. Participants

This study took place in 2014 and included 15 OCD patients (10 female; age median (interquartile range) 30.0(14.0) years [21-44 years]; education 12.0(6.0) years [6-17 years]) recruited at *Hospital de Braga* based on the diagnosis established by a psychiatrist (PMorg) using a semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Patients meeting the criteria for additional Axis I disorders were excluded. All patients were taking selective serotonin reuptake inhibitors and 2 patients were also under tricyclic antidepressants. The control group included 14 non-psychiatric participants recruited locally to match the patients' group in age and gender (9 female; age 27.5(25.2) years [24-58 years]; education 17.0(5.2) [11-20 years]). Control participants were selected if they had no history of psychiatric/neurological conditions, traumatic brain lesions, or substance abuse, and were not under psychiatric medication. Participants were included if no fMRI contraindications were present. From an initial group of 34 participants, 5 were excluded because they were unable to complete the fMRI session (2 patients and 2 controls) or the task files were not saved correctly (1 patient). All participants were right-handed except for 1 left-handed control. OCD patients had lower education than controls (Mann-Whitney test U=174.0, p=0.002, Cohen's effect size d=1.3 [large effect]) but no statistically significant differences were found for age (U=129.0, p=0.304, , d=0.4 [small effect]) and gender ratio (Chi-squared test $\chi^2_{(1)}$<0.1, p=0.893, d<0.1 [no effect]). The education level was used as a covariate in the further statistical analyses because FC in networks associated with cognitive regulation and cognitive functioning depends on educational attainment (Panda et al., 2014; Xueyi Shen et al., 2018). We measured weight and height to determine the body mass index (BMI) in our sample. We did not observe statistically significant differences in BMI between the OCD (mean [standard deviation] 25.6±4.1; 4 patients with missing information) and control groups (24.9±3.7) (independent sample t-test $t_{(23)}$=-0.5, p=0.645, d=-0.2 [small effect]).

The study was performed following the Declaration of Helsinki and was approved by Ethics Subcommittee for the Life and Health Sciences of the University of Minho, Portugal, and by Ethics Committee of *Hospital de Braga*, Portugal. All participants signed an informed consent.

b. Psychological scales

The participants were evaluated with the Beck Anxiety Inventory (BAI) (Aaron T Beck et al., 1988; Quintão et al., 2013) and the Beck Depression Inventory (BDI) (A T Beck et al., 1996; Vaz Serra & Abreu, 1973) to study anxiety and depression scores, respectively. We compared the groups with ANCOVA using education as a confound. The Yale-Brown Obsessive Compulsive Scale (YBOCS) (Castro-Rodrigues et al., 2018; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989) was used to evaluate OCD severity in patients and was administered by a psychiatrist (PMorg).

c. Neuroimaging data

i. fMRI task

The task is fully described in our previous work (S. Ferreira, Veiga, et al., 2019) and was adapted from Hutcherson et al. (2012). Food pictures were displayed under three cognitive regulation conditions: indulge, distance, and natural. Participants were instructed to increase or decreased their craving for food during indulge and distance conditions, respectively. For the natural condition, we asked them to allow spontaneous thoughts/feelings. A cue indicated the condition type (2s). After, each food picture was displayed during 4s for cognitive regulation. Lastly, participants had 2s to place a monetary bid for the food item to earn it at the end of the task (0, 1, 2, or 3€) [**Figure 1A**]. The task was presented using the IFIS-SA system (Invivo Corporation, USA). Participants were fasting for 4h before the task to potentiate the food valuation. Before the task, the participants rated all the food pictures (pre-rating score from 1 to 4 on how much they wanted to eat the food). After the task, the participants ate some of the displayed food, selected based on an adapted version of the Becker-DeGroot-Marschak auction (Becker et al., 1964; Plassmann et al., 2007) to ensure truthful valuation during the task.

ii. fMRI acquisition and preprocessing

The participants were scanned on a 1.5T Magnetom Avanto system (Siemens Medical Solutions, Germany) using a 12-channel head coil. The functional acquisition consisted of an echo-planar imaging

sequence (repetition time 2750ms and 3.5×3.5×3.5 mm^3 voxel size) with 30° orientation relative to the anterior-posterior commissure. The anatomical acquisition was a magnetization-prepared rapid acquisition with gradient echo sequence (1×1×1 mm^3 voxel size and repetition time 2.73s) (detailed description in (S. Ferreira, Veiga, et al., 2019)).

The functional images were preprocessed with Statistical Parametric Mapping (SPM) 12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UK) using MATLAB R2018a (The MathWorks Inc., USA): slice-timing correction; realignment to mean volume; spatial normalization to Montreal Neurologic Institute (MNI) space and resampling to 2×2×2 mm^3; spatial smoothing (8mm full-width at half-maximum Gaussian kernel); high pass temporal filtering (128s).

iii. fMRI statistical analysis

To analyze whole-brain activity differences between the groups during the task, we created a general linear model (GLM) using the following regressors of interest: cognitive regulation condition (1-distance, 2-natural, and 3-indulge) and the corresponding bid (4-bids after distance trials, 5-bids after natural trials, and 6-bids after indulge trials); 7-cue; 8–interstimulus interval; 9–omission bids; 10–16 motion parameters estimated during the realignment step (Caballero-Gaudes & Reynolds, 2017; S. Ferreira, Veiga, et al., 2019). The bid regressors were parametrically modulated using the bid value.

We defined three mixed-design ANCOVA models: (1) cognitive regulation; (2) bidding/valuation without any modulation; (3) bidding/valuation modulated by the bid value. Group was the between-subject factor and each trial during cognitive regulation (distance, natural, indulge) was the within-subject factor. Education was inserted as a covariate. We implemented the models with the GLMFlex toolbox (http://nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/GLM_Flex.html). The results were considered statistically significant after correcting for multiple comparisons with cluster correction (minimum cluster size 74 voxels, 3DClustSim [https://afni.nimh.nih.gov/; AFNI version 17.0.13; National Institute of Mental Health; corrected significance $p<0.05$; initial voxel-wise threshold $p<0.001$]). The SPM AAL plugin was used to classify the statistically significant brain regions (S. Ferreira, Veiga, et al., 2019).

iv. FC analysis

We also studied the FC of the dlPFC and vmPFC during the task by performing generalized psychophysiological (gPPI) analyses (D. G. McLaren et al., 2012). We defined four seed regions with 10mm radius based on the results from Hutcherson et al. (2012): right (MNI 6, 39, 0) and left (MNI -6, 39, 0) dlPFC and right (MNI 48, 36, 24) and left (MNI -48, 36, 24) vmPFC. We estimated the gPPI beta maps for the task conditions (distance, natural, and indulge) during cognitive regulation and bidding. The GLMFlex toolbox was used to calculate differences between groups in FC using the ANCOVA models 1 (cognitive regulation) and 2 (bidding/valuation during the task) described above (minimum cluster size of 74 voxels to correct for multiple comparisons). Model 3 containing regressors with parametric modulators was not supported by the gPPI toolbox.

To estimate the direct effects of each task condition on the seeds' FC, we computed the following contrasts during the gPPI analysis: Distance>Natural, Distance<Natural, Indulge>Natural, Indulge<Natural, Distance>Indulge, and Distance<Indulge for cognitive regulation and bidding. Differences between groups for these contrasts were evaluated in GLMflex using ANCOVA with education as covariate (minimum cluster size of 74 voxels to correct for multiple comparisons) (Do & Telzer, 2019; Humbert & McLaren, 2014; Olivé et al., 2015).

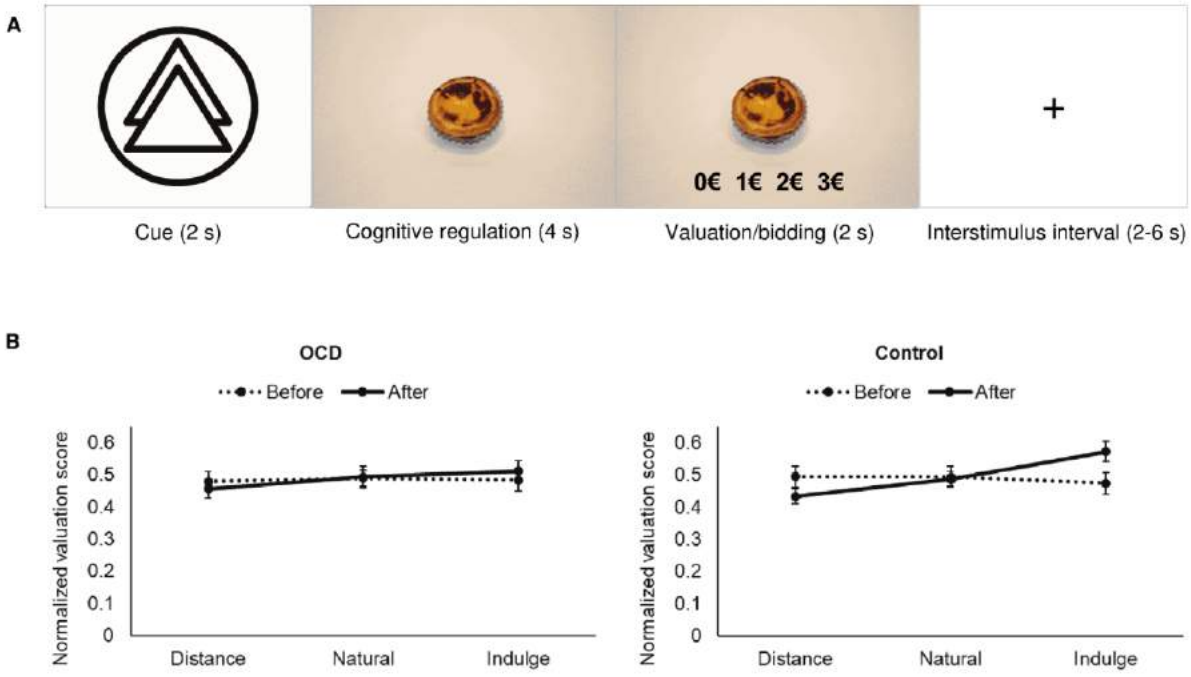


Figure 1 (A) Representation of a trial from the functional magnetic resonance task. A cue indicating the instruction (distance, natural, or indulge) was presented. After a food item picture was displayed and participants had to cognitively regulate their craving accordingly to the cue (distance - downregulation; natural - no regulation; indulge - upregulation). Lastly, participants were asked to give a monetary value to the food item in accordance with their craving (from 0 to 3 €). A total of 150 food pictures was presented; **(B)** Food valuation scores for the control and obsessive-compulsive (OCD) groups. Normalized rating scores for food pictures for each trial condition (natural, distance, and indulge) before performing the functional magnetic resonance task (before cognitive regulation) and during the functional magnetic resonance task (after cognitive regulation). On average, the OCD group valuated the food equally for all conditions, but the scores differed from indulge to distance and natural trials in the control group (**Table 1**). The points represent the mean and the error bars represent the standard error.

d. Statistical analysis

Psychological, demographic, and behavioral data were analyzed with JASP [version 0.9.2; JASP Team (2018), The Netherlands]. Differences were considered statistically significant if $p<0.05$ and the Cohen's d effect size was estimated for all statistically significant results ($0.2\leq d<0.5$ small effect; $0.5\leq d<0.8$ medium effect; $d\geq 0.8$ large effect) (J. Cohen, 1988). We assessed the assumptions of normality (Shapiro-Wilk's test) and homogeneity of variances (Levene's test) in each group. The differences between groups for the parametric variables were estimated with the independent sample *t*-test, ANCOVA, and mixed-design ANCOVA (F test). Post-hoc tests for statistically significant within-subjects (*t*-test) and interaction effects (repeated measures ANOVA) were performed with Bonferroni correction for multiple comparisons ($p_{corrected}$). The Mann-Whitney U test was applied for non-parametric variables.

4. Results

a. Psychological data

OCD patients presented higher anxiety and depression scores than control participants (**Table 1** contains the information about the statistical tests and the average values per group). YBOCS total score in the OCD group ranged from 12.0 to 35.0 [moderate to extreme; 28.0(9.5); obsessions 15.0(5.0); compulsions 13.0(5.0)].

Table 1 Mean values per group and results for statistical tests on psychological scales and behavioral variables associated with the functional magnetic resonance imaging task.

	OCD	Control	Statistical effect	Test value	*P* value	Cohen's *d* effect size
Anxiety (BAI)	28.3 ± 12.0	6.1 ± 3.6	Group	$F_{(1, 26)} = 20.9$	$p < 0.001$	[1]$d = 1.7$ (large)
			Education	$F_{(1, 26)} = 3.5$	$p = 0.074$	$d = 0.5$ (medium)
Depression (BDI)	18.5 ± 13.7	3.8 ± 2.8	Group	$F_{(1, 26)} = 5.2$	$p = 0.031$	[1]$d = 0.8$ (large)
			Education	$F_{(1, 26)} = 3.6$	$p = 0.070$	$d = 0.7$ (medium)
Reaction time (ms)	Distance 813.8 ± 192.0 Natural 753.1 ± 191.4 Indulge 784.9 ± 161.3	Distance 770.3 ± 203.5 Natural 690.5 ± 170.0 Indulge 745.1 ±197.3	Condition (distance, natural, and indulge)	[2]$F_{(1.5, 40.2)} = 0.4$	$p = 0.618$	$d = 0.1$ (no effect)
			Group × Condition	[2]$F_{(1.5, 40.2)} = 0.2$	$p = 0.736$	$d = 0.1$ (no effect)
			Group	$F_{(1, 26)} = 0.6$	$p = 0.445$	$d = 0.3$ (small)
			Education	$F_{(1, 26)} = 0.1$	$p = 0.762$	$d = 0.1$ (no effect)
Valuation score (normalized)	Before cognitive regulation Distance 0.48 ± 0.11 Natural 0.48 ± 0.13 Indulge 0.49 ± 0.10	Before cognitive regulation Distance 0.49 ± 0.12 Natural 0.47 ± 0.13 Indulge 0.49 ± 0.12	Time (before and after cognitive regulation)	$F_{(1, 26)} = 0.2$	$p = 0.683$	$d = 0.1$ (no effect)
			Group × time	$F_{(1, 26)} = 1.7 \times 10^{-2}$	$p = 0.892$	$d < 0.1$ (no effect)
			Condition	$F_{(2, 52)} = 2.8$	$p = 0.064$	$d = 0.2$ (small)
			Group × condition	$F_{(2, 52)} = 3.5$	$p = 0.036$	[1]$d = 0.2$ (small)
	After cognitive regulation Distance 0.46 ± 0.11 Natural 0.49 ± 0.13 Indulge 0.51 ± 0.12	After cognitive regulation Distance 0.43 ± 0.08 Natural 0.49 ± 0.08 Indulge 0.57 ± 0.12	Time × condition	[2]$F_{(1.3, 33.7)} = 1.3$	$p = 0.273$	$d = 0.1$ (no effect)
			Group × time × condition	[2]$F_{(1.3, 33.7)} = 1.3$	$p = 0.273$	$d = 0.1$ (no effect)
			Group	$F_{(1, 26)} = 0.2$	$p = 0.631$	$d = 0.2$ (small)
			Education	$F_{(1, 26)} = 0.3$	$p = 0.558$	$d = 0.2$ (small)
Response frequency	Distance 0 € 23.20 ± 12.12 1 € 13.27 ± 7.01 2 € 7.73 ± 5.39 3 € 3.53 ± 4.17	Distance 0 € 21.93 ± 8.92 1 € 19.00 ± 7.80 2 € 7.21 ± 7.07 3 € 0.78 ± 1.53	Condition	[2]$F_{(1.5, 39.6)} = 0.3$	$p = 0.706$	$d < 0.1$ (no effect)
			Group × condition	[2]$F_{(1.5, 39.6)} = 0.9$	$p = 0.429$	$d < 0.1$ (no effect)
			Valuation (0, 1, 2, and 3 €)	[2]$F_{(1.9, 50.3)} = 1.3$	$p = 0.274$	$d = 0.4$ (small)
			Group × valuation	[2]$F_{(1.9, 50.3)} = 1.5$	$p = 0.240$	$d = 0.4$ (small)
			Condition × valuation	[2]$F_{(3.5, 90.3)} = 1.5$	$p = 0.224$	$d = 0.2$ (small)
			Group × condition × valuation	[2]$F_{(3.5, 90.3)} = 1.5$	$p = 0.202$	$d = 0.2$ (small)

Table 1 continues in the next page

Table 1 Mean values per group and results for statistical tests on psychological scales and behavioral variables associated with the functional magnetic resonance imaging task.

	Natural	Natural	Group	$F_{(1, 26)} = 0.6$	$p = 0.436$	$d < 0.1$ (no effect)
	0 € 19.20 ± 13.10	0 € 17.00 ± 8.27				
	1 € 15.40 ± 7.94	1 € 19.71 ± 8.12				
	2 € 8.53 ± 4.88	2 € 9.14 ± 5.17				
	3 € 4.80 ± 5.94	3 € 2.50 ± 4.60				
	Indulge	Indulge	Education	$F_{(1, 26)} = 0.3$	$p = 0.616$	$d < 0.1$ (no effect)
	0 € 16.93 ± 12.41	0 € 10.07 ± 8.03				
	1 € 16.87 ± 10.05	1 € 19.43 ± 9.34				
	2 € 9.73 ± 6.55	2 € 14.79 ± 8.51				
	3 € 4.73 ± 5.95	3 € 4.71 ± 6.83				

The values represent mean ± standard deviation; [1]Statistical significance; [2]Greenhouse-Geisser correction for non-sphericity. BAI - Beck Anxiety Inventory; BDI - Beck Depression Inventory

b. Behavioral analysis

The task behavioral data were analyzed with mixed-designed ANCOVAs using the group as between-subject factor, condition (distance, natural, and indulge), time (before [pre-fMRI value] and after cognitive regulation [bidding value]), and valuation score (0-3€) as within-subject factors, and education level as a covariate (more details on **Table 1**). To be able to compare the scores before and after cognitive regulation given their different scale, we normalized the scores between 0 and 1 by dividing by the maximum value allowed (4 or 3 € for before and after, respectively).

We did not find statistically significant results between and within-group nor interaction effects for reaction time (**Figure S1**) and the number of responses (response frequency) for each valuation score (**Figure S2**). The valuation score distribution across the conditions was distinct between groups (group×condition interaction; **Table 1**). Post-hoc tests with repeated measures ANOVA showed that only the control group had different valuation scores after each condition (control-condition effect $F_{(2, 28)}$=11.0, $p_{corrected}$=0.001, d=1.8 [large effect]; OCD-condition effect $F_{(2, 28)}$=3.7, $p_{corrected}$=0.077, d=1.0 [large effect]). Post-hoc paired t-tests demonstrated that the value for food after indulge trials was higher than after distance ($t_{(13)}$=-4.5, $p_{corrected}$=0.002, d=1.2 [large effect]) and natural conditions ($t_{(13)}$=-3.3, $p_{corrected}$=0.018, d=0.9 [large effect]), and no significant difference was found between distance and natural trials ($t_{(13)}$=-1.1, $p_{corrected}$=0.862, d=0.3 [small effect]) for control participants (**Figure 1B**).

c. Neuroimaging data

We did not find statistically significant results for the whole-brain activity for the main effect of group, condition, and the interaction between group and condition during cognitive regulation (model 1) and during food valuation/bidding (models 2 and 3).

During cognitive regulation (model 1), the OCD group had increased overall FC (group effect) between the left dlPFC and middle cingulate and left parietal cortical regions (**Figure 2** and **Table 2**). Moreover, both groups showed overall statistically significant FC between the right dlPFC and left occipital, left parahippocampal, and left cerebellar regions (condition effect; **Figure S3**). During food valuation (model 2), we saw augmented overall FC between the left vmPFC and right temporoparietal and right posterior cingulate areas in OCD patients (group effect; **Figure S4** and **Table S1**).

Regarding contrasts' analysis (**Table 2**), during cognitive regulation, we also observed increased FC in the OCD group between the left dlPFC and the right insula and right temporal regions for Distance>Indulge. Furthermore, the left vmPFC had higher connectivity with the right insula and right parietal areas in OCD participants for Distance>Natural (**Figure 2**). During bidding/valuation, we saw increased FC between the left dlPFC and right posterior cingulate, right parietal, and occipital regions for Distance>Natural, and between the left dlPFC and right thalamus, left anterior cingulate and left frontal regions for Indulge>Natural (**Figure S4** and **Table S1**).

Table 2 Regions with differential functional connectivity between the control and obsessive-compulsive disorder groups during cognitive regulation, using the ventromedial and dorsolateral prefrontal cortical seeds ($p < 0.001$, minimum cluster size of 74 voxels).

Brain regions	Cluster size (voxels)	MNI peak voxel coordinates	Peak voxel intensity	Cohen's *d* effect size
Seed - L dlPFC				
OCD > control				
Distance + Natural + Indulge (group main effect)				
L, R Middle cingulate gyrus (BA 23 and 24)	79	-4 -18 26	$F_{(2, 54)} = 5.4$	$d = 0.9$ (large)
L Inferior parietal lobe (BA 40), L Supramarginal gyrus, L Angular gyrus	193	-48 -56 38	$F_{(2, 54)} = 5.4$	$d = 0.9$ (large)
Distance > Indulge				
R Insula (BA 13), R Transverse/superior temporal gyrus, R Heschl's gyrus (BA 41)	107	40 -24 12	$t_{(18)} = 8.2$	$d = 3.0$ (large)
Seed - L vmPFC				
OCD > control				
Distance > Natural				
R Inferior parietal lobe, R Postcentral gyrus (BA 2), R Supramarginal gyrus, R Insula (BA 13), R Rolandic operculum	76	48 -26 32	$t_{(18)} = 6.2$	$d = 2.3$ (large)

MNI - Montreal Neurologic Institute; L - Left; R - Right; dlPFC - dorsolateral prefrontal cortex; vmPFC - ventromedial prefrontal cortex; OCD – obsessive-compulsive disorder; BA – Brodmann area.

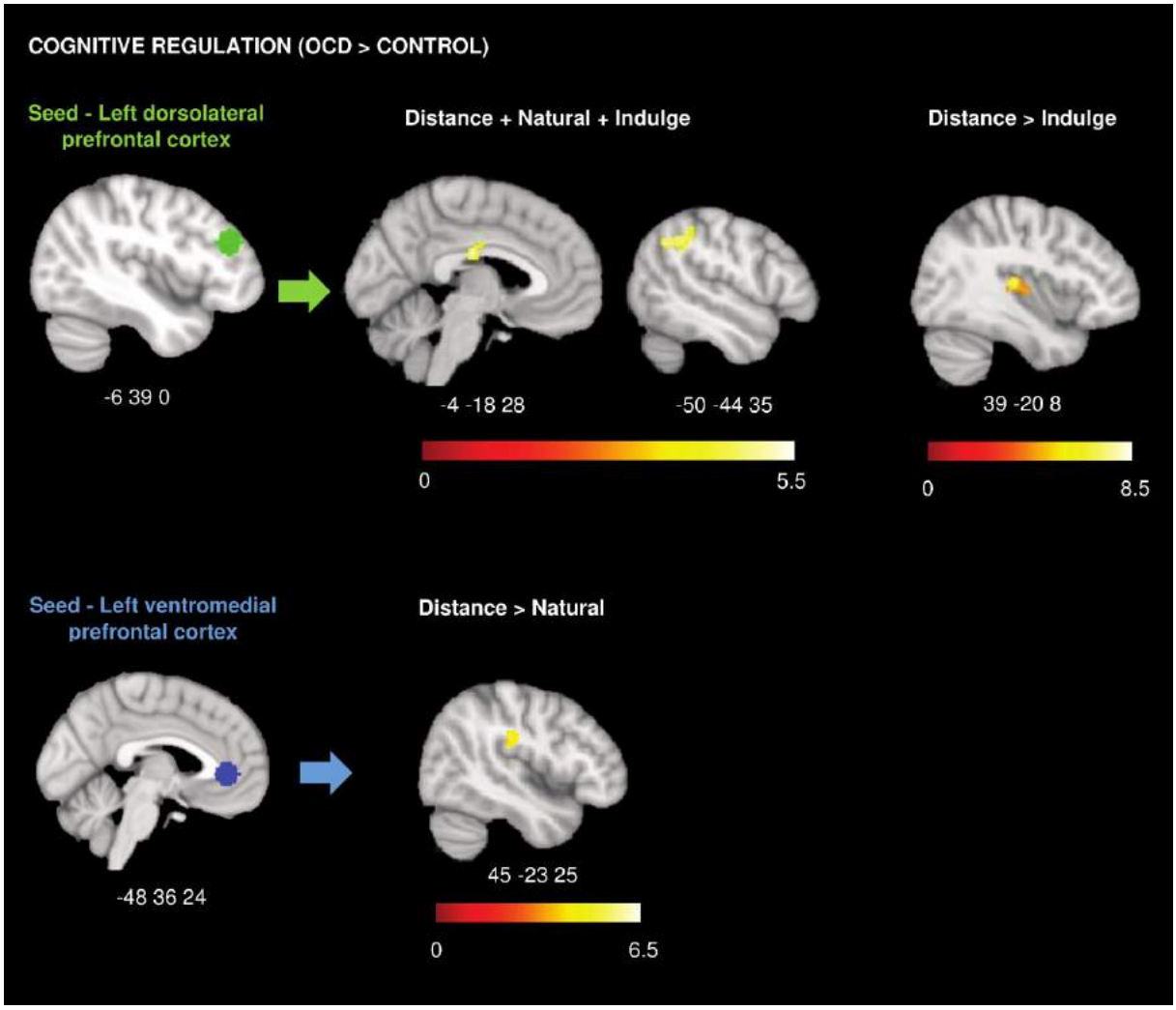


Figure 2 Representation of the functional connectivity differences between groups for cognitive regulation during the task (p<0.001, minimum cluster size 74). The obsessive-compulsive group (OCD) showed increased functional connectivity between the represented regions and the left dorsolateral and ventromedial prefrontal cortices (detailed description in **Table 2**). The colored bar represents the *t*-test or *F*-test values and the Montreal Neurological Institute coordinates are indicated below the brain maps.

d. Correlation analysis

We performed an exploratory analysis to study correlations between the FC in the statistically significant brain regions and psychological variables (BAI and BDI scores; YBOCS total score, YBOCS obsessions score, and YBOCS compulsions score for the OCD group), and the task behavioral parameters (mean reaction time and average valuation score after each regulation condition). We also assessed if behavioral parameters were correlated with psychological scores. The FC values from each region were extracted with SPM functions. We selected non-parametric Spearman correlations because some variables were not normally distributed and/or had a non-homogeneous variance within the group. The correlations were performed including all participants. Post-hoc correlations were computed per group for statistically significant correlations. Bonferroni correction was applied to correct for multiple comparisons ($p_{corrected}$).

We found a positive correlation between the BAI score and FC between the left dlPFC and the right thalamus for the contrast Indulge>Natural during food valuation (model 2; rho=0.5, p=0.005, $p_{corrected}$=0.045, d=1.1 [large effect]; **Figure S4**). Post-hoc correlations for the OCD (rho=-0.2, p=0.398, d=-0.4 [small effect]) and control (rho=0.2, p=0.501, d=0.4 [small effect]) groups did not reach statistical significance.

5. Discussion

Deficits in cognitive regulation of intrusive thoughts and subsequent distressful states in OCD patients may lead to the execution of rewarding compulsions. To characterize these deficits, we studied how the cognitive regulation to increasing/indulge or decreasing/distance craving influences reward valuation in OCD patients. We focused our discussion on the group differences for the neuroimaging findings during cognitive regulation and the subsequent behavior during reward valuation.

We found that OCD patients fail to modulate food valuation scores accordingly to the cognitive regulation condition. These results suggest behavioral flexibility impairments after cognitive regulation of craving and do not agree with our hypothesis of increased reward sensitivity associated with cognitive regulation deficits. A recent meta-analysis did not observe evidence of inflexibility in obsessive-compulsive patients (Fradkin et al., 2018). However, this meta-analysis did not incorporate tasks involving self-directed flexibility similarly to our task and did not focus on reward-related stimuli. Indeed, previous studies

found that OCD individuals can learn stimulus-response associations but have difficulty in altering their behavior when the response-outcome relationship changes in reward-related contexts (Gillan et al., 2011; Nielen et al., 2009; O'Brien et al., 2019; Remijnse et al., 2006; Rouhani et al., 2019; Voon et al., 2015). However, other researchers found contradictory results (Kanen et al., 2019). Animal studies also support behavioral inflexibility in OCD with reward-related tasks (Simmler & Ozawa, 2019). Additionally, the interaction between reward-related attention and cognitive inflexibility predicts increased compulsivity behaviors in individuals with obsessive-compulsive symptoms (Albertella et al., 2020). Furthermore, the severity of compulsions is associated with enhanced habitual learning of reward outcomes (Voon et al., 2015). Thus, our results suggest that OCD is characterized by reward valuation inflexibility after cognitive regulation.

Importantly, OCD patients may show delayed responses to anticipated rewards, suggesting less motivation for rewards (Figee et al., 2011; Kaufmann et al., 2013; Pushkarskaya et al., 2019). However, past research arrived at inconclusive results regarding the impact of OCD on food rewarding sensitivity. Some authors suggest that the repetitive compulsive behaviors to alleviate distress lead to anhedonia (Abramovitch et al., 2014; Abramovitch, Anholt, et al., 2019), while others indicate that OCD symptoms predict higher hedonic hunger during adolescence (Mason et al., 2020). Moreover, other authors saw that OCD is characterized by impairments in consummatory pleasure but not on anticipatory pleasure (S. Li et al., 2019). Nonetheless, our results did not demonstrate decreased BMI or reduced food valuation scores in the OCD group (also before cognitive regulation); thus, anhedonia or lack of motivation is unlikely to explain these results. In this way, our findings suggest that OCD patients are inflexible during reward valuation after cognitive regulation but do not show altered reward sensitivity.

OCD studies combining reward processing tasks and fMRI demonstrated decreased activity in the ventral striatum and prefrontal/cingulate regions during reward anticipation (Figee et al., 2011; Kaufmann et al., 2013; Marsh et al., 2015) and reward processing (Koch et al., 2018; Remijnse et al., 2006), and in the orbitofrontal cortex, insula, and dlPFC during affective switching (Remijnse et al., 2006), although other authors found unaltered brain responses during reward anticipation (Choi et al., 2012). Recent research with FC analyses showed increased vmPFC-orbitofrontal connectivity during reward learning (Alves-Pinto et al., 2019) and vmPFC-posterior cingulate connectivity during reward processing (Koch et al., 2018). Although we did not find alterations in brain activity, the increased FC between vmPFC and posterior cingulate regions during reward valuation agree with the past literature exploring reward processing deficits in OCD.

During cognitive regulation, we observed increased FC between the left dlPFC and middle cingulate and left inferior parietal cortical regions in OCD patients. The dlPFC and inferior parietal cortex are part of the network for selective attention and working memory processes during goal-directed emotional reappraisal (Ochsner et al., 2012). The FPN presents higher activity when attention is focused on external stimuli (Stern et al., 2012, 2017), being involved in top-down attentional and cognitive control (Fan et al., 2018). Rest FC between the left medial prefrontal cortex and the right inferior parietal lobe/angular gyrus is positively associated with sustained attention deficits in OCD (Fan et al., 2018). Moreover, the FPN is now pointed as one of the main circuits underlying OCD regarding cognitive control (Stein et al., 2019).

While decreasing craving, we saw increased connections in OCD participants between the left dlPFC and the right insula and right temporal areas when compared to increasing craving, and between the left vmPFC and the right insula and right inferior parietal regions when compared to the non-regulated condition. Our results were only related to the distance condition. Thus, decreasing craving might be more cognitively demanding than increasing it while visualizing food images emphasizing group differences in FC between controls and OCD (Ochsner et al., 2012). The vmPFC integrates the valuation of stimuli (Ochsner et al., 2012). The insula mediates sensory inputs and body functions (Del Casale et al., 2016) and is modulated by emotional reappraisal and suppression (Gonçalves et al., 2016; Ochsner et al., 2012). Additionally, it is involved in the selection of adequate emotional reappraisal strategies by engaging prefrontoparietal regions to diminish amygdalar responses (Maria Picó-Pérez et al., 2019). The insula is also part of the salience network which is engaged during external attentional demands and has increased FC during cognitive control tasks in OCD (Cocchi et al., 2012). Moreover, the augmented connectivity between the medial prefrontal cortex and right anterior insula is associated with decreased sustained attention (Posner et al., 2017) and enhanced error-related responses (Stern et al., 2011) in OCD.

We did not observe dysfunctional responses in FPN and associated regions in the OCD group during cognitive regulation. Thus, our study might be underpowered to detect differences in whole-brain responses. Indeed, earlier studies showed that OCD is characterized by decreased brain responses in prefrontal, parietal, insular, and cingulate regions during tasks requiring cognitive control (Eng et al., 2015; Gonçalves et al., 2016; Koçak et al., 2011; Stern & Taylor, 2014) in agreement with the regions resulting from our FC analysis. The allocation of attention and control mechanisms during emotional regulation is also impaired in anxiety disorders and is underlined by reduced FPN and cingulate activity (Zilverstand et al., 2017).

In conclusion, increased FC between regions within the FPN and between prefrontal and insular areas in OCD suggests the engagement of compensatory mechanisms to maintain efficiency during cognitive

regulation (de Vries et al., 2019). OCD patients may require stronger attentional effort to switch between disorder-related internal states to external goals (Y. Chen et al., 2016; Cocchi et al., 2012; de Vries et al., 2019; Del Casale et al., 2016; Koçak et al., 2011; Norman et al., 2017; Stern et al., 2017; Stern & Taylor, 2014). Thus, our results might indicate a failure in insular/salience network modulation of the FPN, suggesting an impairment in deviating top-down control of attention from obsessions in the presence of external stimuli (Fan et al., 2017; Tomiyama et al., 2019). However, previous studies also found that OCD patients and individuals with high obsessive-compulsive symptoms have difficulty in accessing internal states such as emotions and bodily states/sensations, including hunger (Lazarov et al., 2012, 2014, 2015; Liberman & Dar, 2018). Thus, our findings might result from a deficiency in accessing the internal sensation of craving rather than cognitive regulation impairments. The patients might be unable to detect variations in craving to regulate it. In this way, more research must be conducted to disentangle these two hypotheses: (1) the presence of intrusive thoughts and anxiety/distress limits the available cognitive resources; (2) the restrained access to internal states prevents effective cognitive regulation.

Our conclusions are limited by the sample size. The task selected for this study is specific to cognitive regulation of food craving. In this way, our conclusions may not generalize to other domains of cognitive regulation of reward. Moreover, we cannot rule out the putative effects of medication and co-morbidity status in our results. Antidepressant medication can affect the function and FC of brain pathways and the behavior associated with cognitive regulation (Carthy et al., 2017; Outhred et al., 2013; Wagner et al., 2017). Future studies should include treatment naïve patients or address changes in cognitive regulation of reward before and after treatment. Lastly, the generalizability of our results is limited to OCD individuals without comorbidities.

6. Conclusions

Although further research is required, our results bring new insights into the understanding of OCD mechanisms. FPN hyperconnectivity during cognitive regulation of internal states is associated with inflexible behavior during reward anticipation and not linked to altered reward sensitivity. Thus, OCD compulsive behavior might not be a result of increased anticipatory rewarding value.

7. Funding

This study was funded by the MyHealth project (DoIT - *Desenvolvimento e Operacionalização da Investigação de Translação*, Contract DoIT-13853). This study was also funded by FEDER funds, through the Competitiveness Factors Operational Programme (COMPETE), and by National funds, through the Foundation for Science and Technology (FCT), under the scope of the project POCI-01-0145-FEDER-007038. This article has been developed under the scope of the project NORTE-01-0145-FEDER-000013, supported by the Northern Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020 Partnership Agreement, through the European Regional Development Fund (FEDER). PM was supported by a fellowship of the project "SwitchBox" (grant number HEALTH-F2-2010-259772). SF was supported by a combined Ph. D. scholarship from FCT and the company iCognitus4ALL - IT Solutions, Lda (grant number PD/BDE/127839/2016). RM was supported by the combined FCT and Enlightenment, Lda fellowship (grant number PDE/BDE/113604/2015) from the PhDiHES program. The funding sources had no specific role in the development of the research work and the preparation of the manuscript.

8. References

Abe, Y., Sakai, Y., Nishida, S., Nakamae, T., Yamada, K., Fukui, K., & Narumoto, J. (2015). Hyper-influence of the orbitofrontal cortex over the ventral striatum in obsessive-compulsive disorder. European Neuropsychopharmacology, 25(11), 1898–1905. https://doi.org/10.1016/j.euroneuro.2015.08.017

Abramovitch, A., Anholt, G. E., Cooperman, A., van Balkom, A. J. L. M., Giltay, E. J., Penninx, B. W., & van Oppen, P. (2019). Body mass index in obsessive-compulsive disorder. Journal of Affective Disorders, 245(June 2018), 145–151. https://doi.org/10.1016/j.jad.2018.10.116

Abramovitch, A., Pizzagalli, D. A., Reuman, L., & Wilhelm, S. (2014). Anhedonia in obsessive-compulsive disorder: Beyond comorbid depression. Psychiatry Research, 216(2), 223–229. https://doi.org/10.1016/j.psychres.2014.02.002

Adriani, W., Koot, S., Columba-Cabezas, S., Romano, E., Travaglini, D., van den Bos, R., Granstrem, O., Ali, S. F., & Laviola, G. (2012). Immunization with DAT fragments is associated with long-term striatal impairment, hyperactivity and reduced cognitive flexibility in mice. Behavioral and Brain Functions, 8(1), 54. https://doi.org/10.1186/1744-9081-8-54

Albertella, L., Le Pelley, M. E., Chamberlain, S. R., Westbrook, F., Fontenelle, L. F., Segrave, R., Lee, R., Pearson, D., & Yücel, M. (2019). Reward-related attentional capture is associated with severity of addictive

and obsessive–compulsive behaviors. Psychology of Addictive Behaviors, 33(5), 495–502. https://doi.org/10.1037/adb0000484

Albertella, L., Le Pelley, M. E., Chamberlain, S. R., Westbrook, F., Lee, R. S. C., Fontenelle, L. F., Grant, J. E., Segrave, R., McTavish, E., & Yücel, M. (2020). Reward-related attentional capture and cognitive inflexibility interact to determine greater severity of compulsivity-related problems. Journal of Behavior Therapy and Experimental Psychiatry, 101580. https://doi.org/10.1016/j.jbtep.2020.101580

Alves-Pinto, A., Rus, O. G., Reess, T. J., Wohlschläger, A., Wagner, G., Berberich, G., & Koch, K. (2019). Altered reward-related effective connectivity in obsessive-compulsive disorder: an fMRI study. Journal of Psychiatry and Neuroscience, 44(6), 395–406. https://doi.org/10.1503/jpn.180195

American Psychiatric Association. (2013). Diagnostic Statistical Manual of Mental Disorders (DSM-5). In American Psychiatric Association (5th, revised ed.). American Psychiatric Association Pub, 2013.

Amidfar, M., Ko, Y.-H., & Kim, Y.-K. (2019). Neuromodulation and Cognitive Control of Emotion (pp. 545–564). https://doi.org/10.1007/978-981-32-9721-0_27

Banca, P., Voon, V., Vestergaard, M. D., Philipiak, G., Almeida, I., Pocinho, F., Relvas, J., & Castelo-Branco, M. (2015). Imbalance in habitual versus goal directed neural systems during symptom provocation in obsessive-compulsive disorder. Brain, 138(3), 798–811. https://doi.org/10.1093/brain/awu379

Beck, A T, Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. Journal of Personality Assessment, 67(3), 588–597. https://ci.nii.ac.jp/naid/10025577512/en/

Beck, Aaron T, Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. Journal of Consulting and Clinical Psychology, 56(6), 893–897. https://doi.org/10.1037/0022-006X.56.6.893

Becker, G. M., Degroot, M. H., & Marschak, J. (1964). Measuring utility by a single-response sequential method. Behavioral Science, 9(3), 226–232. https://doi.org/10.1002/bs.3830090304

Brandl, F., Le Houcq Corbi, Z., Mulej Bratec, S., & Sorg, C. (2019). Cognitive reward control recruits medial and lateral frontal cortices, which are also involved in cognitive emotion regulation: A coordinate-based meta-analysis of fMRI studies. NeuroImage, 200(August 2018), 659–673. https://doi.org/10.1016/j.neuroimage.2019.07.008

Caballero-Gaudes, C., & Reynolds, R. C. (2017). Methods for cleaning the BOLD fMRI signal. NeuroImage, 154(December 2016), 128–149. https://doi.org/10.1016/j.neuroimage.2016.12.018

Carthy, T., Benaroya-Milshtein, N., Valevski, A., & Apter, A. (2017). Emotional Reactivity and Regulation Following Citalopram Therapy in Children and Adolescents with Anxiety Disorders. Journal of Child and Adolescent Psychopharmacology, 27(1), 43–51. https://doi.org/10.1089/cap.2015.0067

Castro-Rodrigues, P., Camacho, M., Almeida, S., Marinho, M., Soares, C., Barahona-Corrêa, J. B., & Oliveira-Maia, A. J. (2018). Criterion Validity of the Yale-Brown Obsessive-Compulsive Scale Second Edition for Diagnosis of Obsessive-Compulsive Disorder in Adults. Frontiers in Psychiatry, 9(SEP), 1–10. https://doi.org/10.3389/fpsyt.2018.00431

Chen, Y., Meng, X., Hu, Q., Cui, H., Ding, Y., Kang, L., Juhás, M., Greenshaw, A. J., Zhao, A., Wang, Y., Cui, G., & Li, P. (2016). Altered resting-state functional organization within the central executive network in obsessive-compulsive disorder. Psychiatry and Clinical Neurosciences, 70(10), 448–456. https://doi.org/10.1111/pcn.12419

Choi, J.-S., Shin, Y.-C., Jung, W. H., Jang, J. H., Kang, D.-H., Choi, C.-H., Choi, S.-W., Lee, J.-Y., Hwang, J. Y., & Kwon, J. S. (2012). Altered Brain Activity during Reward Anticipation in Pathological Gambling and Obsessive-Compulsive Disorder. PLoS ONE, 7(9), e45938. https://doi.org/10.1371/journal.pone.0045938

Cinque, S., Zoratto, F., Poleggi, A., Leo, D., Cerniglia, L., Cimino, S., Tambelli, R., Alleva, E., Gainetdinov, R. R., Laviola, G., & Adriani, W. (2018). Behavioral Phenotyping of Dopamine Transporter Knockout Rats: Compulsive Traits, Motor Stereotypies, and Anhedonia. Frontiers in Psychiatry, 9(FEB), 43. https://doi.org/10.3389/fpsyt.2018.00043

Cocchi, L., Harrison, B. J., Pujol, J., Harding, I. H., Fornito, A., Pantelis, C., & Yücel, M. (2012). Functional alterations of large-scale brain networks related to cognitive control in obsessive-compulsive disorder. Human Brain Mapping, 33(5), 1089–1106. https://doi.org/10.1002/hbm.21270

Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. Trends in Cognitive Sciences, 17(10), 493–501. https://doi.org/10.1016/j.tics.2013.08.006

Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Lawrence Erlbaum Associates.

Cutuli, D. (2014). Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Frontiers in Systems Neuroscience, 8(September), 1–6. https://doi.org/10.3389/fnsys.2014.00175

de Vries, F. E., de Wit, S. J., van den Heuvel, O. A., Veltman, D. J., Cath, D. C., van Balkom, A. J. L. M., & van der Werf, Y. D. (2019). Cognitive control networks in OCD: A resting-state connectivity study in unmedicated patients with obsessive-compulsive disorder and their unaffected relatives. The World Journal of Biological Psychiatry, 20(3), 230–242. https://doi.org/10.1080/15622975.2017.1353132

De Wit, S. J., Van Der Werf, Y. D., Mataix-Cols, D., Trujillo, J. P., Van Oppen, P., Veltman, D. J., & van den Heuvel, O. A. (2015). Emotion regulation before and after transcranial magnetic stimulation in obsessive compulsive disorder. Psychological Medicine, 45(14), 3059–3073. https://doi.org/10.1017/S0033291715001026

Del Casale, A., Rapinesi, C., Kotzalidis, G. D., De Rossi, P., Curto, M., Janiri, D., Criscuolo, S., Alessi, M. C., Ferri, V. R., De Giorgi, R., Sani, G., Ferracuti, S., Girardi, P., & Brugnoli, R. (2016). Executive functions in obsessive–compulsive disorder: An activation likelihood estimate meta-analysis of fMRI studies. The World Journal of Biological Psychiatry, 17(5), 378–393. https://doi.org/10.3109/15622975.2015.1102323

Demos McDermott, K. E., Lillis, J., McCaffery, J. M., & Wing, R. R. (2019). Effects of Cognitive Strategies on Neural Food Cue Reactivity in Adults with Overweight/Obesity. Obesity, 27(10), 1577–1583. https://doi.org/10.1002/oby.22572

Do, K. T., & Telzer, E. H. (2019). Corticostriatal connectivity is associated with the reduction of intergroup bias and greater impartial giving in youth. Developmental Cognitive Neuroscience, 37, 100628. https://doi.org/10.1016/J.DCN.2019.100628

Dougherty, D. D., Brennan, B. P., Stewart, S. E., Wilhelm, S., Widge, A. S., & Rauch, S. L. (2018). Neuroscientifically Informed Formulation and Treatment Planning for Patients With Obsessive-Compulsive Disorder. JAMA Psychiatry, 75(10), 1081. https://doi.org/10.1001/jamapsychiatry.2018.0930

Eng, G. K., Sim, K., & Chen, S.-H. A. (2015). Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive

disorder: An integrative review. Neuroscience & Biobehavioral Reviews, 52, 233–257. https://doi.org/10.1016/j.neubiorev.2015.03.002

Fan, J., Gan, J., Liu, W., Zhong, M., Liao, H., Zhang, H., Yi, J., Chan, R. C. K., Tan, C., & Zhu, X. (2018). Resting-State Default Mode Network Related Functional Connectivity Is Associated With Sustained Attention Deficits in Schizophrenia and Obsessive-Compulsive Disorder. Frontiers in Behavioral Neuroscience, 12(December). https://doi.org/10.3389/fnbeh.2018.00319

Fan, J., Zhong, M., Gan, J., Liu, W., Niu, C., Liao, H., Zhang, H., Yi, J., Chan, R. C. K., Tan, C., & Zhu, X. (2017). Altered connectivity within and between the default mode, central executive, and salience networks in obsessive-compulsive disorder. Journal of Affective Disorders, 223(June), 106–114. https://doi.org/10.1016/j.jad.2017.07.041

Fernández de la Cruz, L., Landau, D., Iervolino, A. C., Santo, S., Pertusa, A., Singh, S., & Mataix-Cols, D. (2013). Experiential avoidance and emotion regulation difficulties in hoarding disorder. Journal of Anxiety Disorders, 27(2), 204–209. https://doi.org/10.1016/j.janxdis.2013.01.004

Ferreira, G. M., Lee, R. S. C., Piquet-Pessôa, M., de Menezes, G. B., Moreira-de-Oliveira, M. E., Albertella, L., Yücel, M., dos Santos Cruz, M., dos Santos-Ribeiro, S., & Fontenelle, L. F. (2020). Habitual versus affective motivations in obsessive-compulsive disorder and alcohol use disorder. CNS Spectrums, 1–8. https://doi.org/10.1017/S1092852919001706

Ferreira, G. M., Yücel, M., Dawson, A., Lorenzetti, V., & Fontenelle, L. F. (2017). Investigating the role of anticipatory reward and habit strength in obsessive-compulsive disorder. CNS Spectrums, 22(3), 295–304. https://doi.org/10.1017/S1092852916000535

Ferreira, S., Veiga, C., Moreira, P., Magalhães, R., Coelho, A., Marques, P., Portugal-Nunes, C., Sousa, N., & Morgado, P. (2019). Reduced Hedonic Valuation of Rewards and Unaffected Cognitive Regulation in Chronic Stress. Frontiers in Neuroscience, 13, 724. https://doi.org/10.3389/fnins.2019.00724

Figee, M., Vink, M., de Geus, F., Vulink, N., Veltman, D. J., Westenberg, H., & Denys, D. (2011). Dysfunctional Reward Circuitry in Obsessive-Compulsive Disorder. Biological Psychiatry, 69(9), 867–874. https://doi.org/10.1016/j.biopsych.2010.12.003

Fink, J., Pflugradt, E., Stierle, C., & Exner, C. (2018). Changing disgust through imagery rescripting and cognitive reappraisal in contamination-based obsessive-compulsive disorder. Journal of Anxiety Disorders, 54(January), 36–48. https://doi.org/10.1016/j.janxdis.2018.01.002

Fradkin, I., Strauss, A. Y., Pereg, M., & Huppert, J. D. (2018). Rigidly Applied Rules? Revisiting Inflexibility in Obsessive Compulsive Disorder Using Multilevel Meta-Analysis. Clinical Psychological Science, 6(4), 481–505. https://doi.org/10.1177/2167702618756069

Gillan, C. M., Apergis-Schoute, A. M., Morein-Zamir, S., Urcelay, G. P., Sule, A., Fineberg, N. A., Sahakian, B. J., & Robbins, T. W. (2015). Functional Neuroimaging of Avoidance Habits in Obsessive-Compulsive Disorder. American Journal of Psychiatry, 172(3), 284–293. https://doi.org/10.1176/appi.ajp.2014.14040525

Gillan, C. M., Morein-Zamir, S., Urcelay, G. P., Sule, A., Voon, V., Apergis-Schoute, A. M., Fineberg, N. A., Sahakian, B. J., & Robbins, T. W. (2014). Enhanced Avoidance Habits in Obsessive-Compulsive Disorder. Biological Psychiatry, 75(8), 631–638. https://doi.org/10.1016/j.biopsych.2013.02.002

Gillan, C. M., Papmeyer, M., Morein-Zamir, S., Sahakian, B. J., Fineberg, N. A., Robbins, T. W., & de Wit, S. (2011). Disruption in the Balance Between Goal-Directed Behavior and Habit Learning in Obsessive-Compulsive Disorder. American Journal of Psychiatry, 168(7), 718–726. https://doi.org/10.1176/appi.ajp.2011.10071062

Gonçalves, Ó. F., Carvalho, S., Leite, J., Fernandes-Gonçalves, A., Carracedo, A., & Sampaio, A. (2016). Cognitive and emotional impairments in obsessive–compulsive disorder: Evidence from functional brain alterations. Porto Biomedical Journal, 1(3), 92–105. https://doi.org/10.1016/j.pbj.2016.07.005

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. II. Validity. Archives of General Psychiatry, 46(11), 1012–1016. http://www.ncbi.nlm.nih.gov/pubmed/2510699

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Archives of General Psychiatry, 46(11), 1006–1011. http://www.ncbi.nlm.nih.gov/pubmed/2684084

Göttlich, M., Krämer, U. M., Kordon, A., Hohagen, F., & Zurowski, B. (2014). Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. Human Brain Mapping, 35(11), 5617–5632. https://doi.org/10.1002/hbm.22574

Grassi, G., Makris, N., & Pallanti, S. (2020). Addicted to compulsion: assessing three core dimensions of addiction across obsessive-compulsive disorder and gambling disorder. CNS Spectrums, 25(3), 392–401. https://doi.org/10.1017/S1092852919000993

Gruner, P., & Pittenger, C. (2017). Cognitive inflexibility in Obsessive-Compulsive Disorder. Neuroscience, 345(August), 243–255. https://doi.org/10.1016/j.neuroscience.2016.07.030

Han, J. E., Boachie, N., Garcia-Garcia, I., Michaud, A., & Dagher, A. (2018). Neural correlates of dietary self-control in healthy adults: A meta-analysis of functional brain imaging studies. Physiology and Behavior, 192, 98–108. https://doi.org/10.1016/j.physbeh.2018.02.037

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-Control in Decision-Making Involves Modulation of the vmPFC Valuation System. Science, 324(5927), 646–648. https://doi.org/10.1126/science.1168450

Humbert, I. A., & McLaren, D. G. (2014). Differential psychophysiological interactions of insular subdivisions during varied oropharyngeal swallowing tasks. Physiological Reports, 2(3), e00239. https://doi.org/10.1002/phy2.239

Hutcherson, C. A., Plassmann, H., Gross, J. J., & Rangel, A. (2012). Cognitive Regulation during Decision Making Shifts Behavioral Control between Ventromedial and Dorsolateral Prefrontal Value Systems. Journal of Neuroscience, 32(39), 13543–13554. https://doi.org/10.1523/JNEUROSCI.6387-11.2012

Jung, W. H., Kang, D.-H., Han, J. Y., Jang, J. H., Gu, B.-M., Choi, J.-S., Jung, M. H., Choi, C.-H., & Kwon, J. S. (2011). Aberrant ventral striatal responses during incentive processing in unmedicated patients with obsessive-compulsive disorder. Acta Psychiatrica Scandinavica, 123(5), 376–386. https://doi.org/10.1111/j.1600-0447.2010.01659.x

Jung, Wi Hoon, Kang, D.-H., Kim, E., Shin, K. S., Jang, J. H., & Kwon, J. S. (2013). Abnormal corticostriatal-limbic functional connectivity in obsessive–compulsive disorder during reward processing and resting-state. NeuroImage: Clinical, 3, 27–38. https://doi.org/10.1016/j.nicl.2013.06.013

Kanen, J. W., Ersche, K. D., Fineberg, N. A., Robbins, T. W., & Cardinal, R. N. (2019). Computational modelling reveals contrasting effects on reinforcement learning and cognitive flexibility in stimulant use disorder and obsessive-compulsive disorder: remediating effects of dopaminergic D2/3 receptor agents. Psychopharmacology, 236(8), 2337–2358. https://doi.org/10.1007/s00213-019-05325-w

Kaufmann, C., Beucke, J. C., Preuße, F., Endrass, T., Schlagenhauf, F., Heinz, A., Juckel, G., & Kathmann, N. (2013). Medial prefrontal brain activation to anticipated reward and loss in obsessive–

compulsive disorder. NeuroImage: Clinical, 2(1), 212–220. https://doi.org/10.1016/j.nicl.2013.01.005

Kober, H., Mende-Siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., & Ochsner, K. N. (2010). Prefrontal-striatal pathway underlies cognitive regulation of craving. Proceedings of the National Academy of Sciences, 107(33), 14811–14816. https://doi.org/10.1073/pnas.1007779107

Koçak, O. M., Özpolat, A. Y., Atbaşoğlu, C., & Çiçek, M. (2011). Cognitive control of a simple mental image in patients with obsessive–compulsive disorder. Brain and Cognition, 76(3), 390–399. https://doi.org/10.1016/j.bandc.2011.03.020

Koch, K., Reeß, T. J., Rus, O. G., Gürsel, D. A., Wagner, G., Berberich, G., & Zimmer, C. (2018). Increased Default Mode Network Connectivity in Obsessive–Compulsive Disorder During Reward Processing. Frontiers in Psychiatry, 9(JUN), 1–9. https://doi.org/10.3389/fpsyt.2018.00254

Langner, R., Leiberg, S., Hoffstaedter, F., & Eickhoff, S. B. (2018). Towards a human self-regulation system: Common and distinct neural signatures of emotional and behavioural control. Neuroscience & Biobehavioral Reviews, 90(1), 400–410. https://doi.org/10.1016/j.neubiorev.2018.04.022

Lazarov, A., Cohen, T., Liberman, N., & Dar, R. (2015). Can doubt attenuate access to internal states? Implications for obsessive-compulsive disorder. Journal of Behavior Therapy and Experimental Psychiatry, 49, 150–156. https://doi.org/10.1016/j.jbtep.2014.11.003

Lazarov, A., Dar, R., Liberman, N., & Oded, Y. (2012). Obsessive-compulsive tendencies and undermined confidence are related to reliance on proxies for internal states in a false feedback paradigm. Journal of Behavior Therapy and Experimental Psychiatry, 43(1), 556–564. https://doi.org/10.1016/j.jbtep.2011.07.007

Lazarov, A., Liberman, N., Hermesh, H., & Dar, R. (2014). Seeking proxies for internal states in obsessive–compulsive disorder. Journal of Abnormal Psychology, 123(4), 695–704. https://doi.org/10.1037/abn0000004

Li, S., Zhang, Y., Fan, J., Liu, W., Gan, J., He, J., Yi, J., Tan, C., & Zhu, X. (2019). Patients With Obsessive-Compulsive Disorder Exhibit Deficits in Consummatory but Not Anticipatory Pleasure. Frontiers in Psychology, 10(MAY), 1–6. https://doi.org/10.3389/fpsyg.2019.01196

Liberman, N., & Dar, R. (2018). Obsessive-compulsive tendencies are related to seeking proxies for internal states in everyday life. Journal of Behavior Therapy and Experimental Psychiatry, 61(November 2017), 164–171. https://doi.org/10.1016/j.jbtep.2018.08.002

Lopez, R. B., Courtney, A. L., & Wagner, D. D. (2019). Recruitment of cognitive control regions during effortful self-control is associated with altered brain activity in control and reward systems in dieters during subsequent exposure to food commercials. PeerJ, 7(2), e6550. https://doi.org/10.7717/peerj.6550

Marsh, R., Tau, G. Z., Wang, Z., Huo, Y., Liu, G., Hao, X., Packard, M. G., Peterson, B. S., & Simpson, H. B. (2015). Reward-Based Spatial Learning in Unmedicated Adults With Obsessive-Compulsive Disorder. American Journal of Psychiatry, 172(4), 383–392. https://doi.org/10.1176/appi.ajp.2014.13121700

Mason, T. B., Dunton, G. F., Gearhardt, A. N., & Leventhal, A. M. (2020). Emotional disorder symptoms, anhedonia, and negative urgency as predictors of hedonic hunger in adolescents. Eating Behaviors, 36(November 2019), 101343. https://doi.org/10.1016/j.eatbeh.2019.101343

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. NeuroImage, 61(4), 1277–1286. https://doi.org/10.1016/j.neuroimage.2012.03.068

Mehl, N., Morys, F., Villringer, A., & Horstmann, A. (2019). Unhealthy yet Avoidable—How Cognitive Bias Modification Alters Behavioral and Brain Responses to Food Cues in Individuals with Obesity. Nutrients, 11(4), 874. https://doi.org/10.3390/nu11040874

Nielen, M. M., den Boer, J. A., & Smid, H. G. O. M. (2009). Patients with obsessive–compulsive disorder are impaired in associative learning based on external feedback. Psychological Medicine, 39(9), 1519–1526. https://doi.org/10.1017/S0033291709005297

Nigg, J. T. (2017). Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. Journal of Child Psychology and Psychiatry, 58(4), 361–383. https://doi.org/10.1111/jcpp.12675

Norman, L. J., Carlisi, C. O., Christakou, A., Cubillo, A., Murphy, C. M., Chantiluke, K., Simmons, A., Giampietro, V., Brammer, M., Mataix-Cols, D., & Rubia, K. (2017). Shared and disorder-specific task-positive and default mode network dysfunctions during sustained attention in paediatric Attention-Deficit/Hyperactivity Disorder and obsessive/compulsive disorder. NeuroImage: Clinical, 15(March), 181–193. https://doi.org/10.1016/j.nicl.2017.04.013

O'Brien, J. L., Jacob, M. L., & King, M. (2019). Preliminary evidence of biased attentional mechanisms and reward processing in adults with obsessive-compulsive disorder. Bulletin of the Menninger Clinic, 83(2), 128–151. https://doi.org/10.1521/bumc.2019.83.2.128

Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Annals of the New York Academy of Sciences, 1251(1), E1–E24. https://doi.org/10.1111/j.1749-6632.2012.06751.x

Olivé, I., Tempelmann, C., Berthoz, A., & Heinze, H.-J. (2015). Increased functional connectivity between superior colliculus and brain regions implicated in bodily self-consciousness during the rubber hand illusion. Human Brain Mapping, 36(2), 717–730. https://doi.org/10.1002/hbm.22659

Outhred, T., Hawkshead, B. E., Wager, T. D., Das, P., Malhi, G. S., & Kemp, A. H. (2013). Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: Implications for differential treatment efficacy. Neuroscience & Biobehavioral Reviews, 37(8), 1786–1800. https://doi.org/10.1016/j.neubiorev.2013.07.010

Panda, R., Bharath, R. D., George, L., Kanungo, S., Reddy, R. P., Upadhyay, N., Thamodharan, A., Rajeshwaran, J., Rao, S. L., & Gupta, A. K. (2014). Unraveling Brain Functional Connectivity of encoding and retrieval in the context of education. Brain and Cognition, 86(1), 75–81. https://doi.org/10.1016/j.bandc.2014.01.018

Paul, S., Simon, D., Endrass, T., & Kathmann, N. (2016). Altered emotion regulation in obsessive-compulsive disorder as evidenced by the late positive potential. Psychological Medicine, 46(1), 137–147. https://doi.org/10.1017/S0033291715001610

Picó-Pérez, M., Ipser, J., Taylor, P., Alonso, P., López-Solà, C., Real, E., Segalàs, C., Roos, A., Menchón, J. M., Stein, D. J., & Soriano-Mas, C. (2019). Intrinsic functional and structural connectivity of emotion regulation networks in obsessive-compulsive disorder. Depression and Anxiety, 36(2), 110–120. https://doi.org/10.1002/da.22845

Plassmann, H., O'Doherty, J., & Rangel, A. (2007). Orbitofrontal Cortex Encodes Willingness to Pay in Everyday Economic Transactions. Journal of Neuroscience, 27(37), 9984–9988. https://doi.org/10.1523/JNEUROSCI.2131-07.2007

Posner, J., Song, I., Lee, S., Rodriguez, C. I., Moore, H., Marsh, R., & Blair Simpson, H. (2017). Increased functional connectivity between the default mode and salience networks in unmedicated adults with obsessive-compulsive disorder. Human Brain Mapping, 38(2), 678–687. https://doi.org/10.1002/hbm.23408

Pruessner, L., Barnow, S., Holt, D. V., Joormann, J., & Schulze, K. (2020). A cognitive control framework for understanding emotion regulation flexibility. Emotion, 20(1), 21–29. https://doi.org/10.1037/emo0000658

Pushkarskaya, H., Sobowale, K., Henick, D., Tolin, D. F., Anticevic, A., Pearlson, G. D., Levy, I., Harpaz-Rotem, I., & Pittenger, C. (2019). Contrasting contributions of anhedonia to obsessive-compulsive, hoarding, and post-traumatic stress disorders. Journal of Psychiatric Research, 109(April 2018), 202–213. https://doi.org/10.1016/j.jpsychires.2018.11.029

Quintão, S., Delgado, A. R., & Prieto, G. (2013). Validity study of the Beck Anxiety Inventory (Portuguese version) by the Rasch Rating Scale model. Psicologia: Reflexão e Crítica, 26(2), 305–310. https://doi.org/10.1590/S0102-79722013000200010

Remijnse, P. L., Nielen, M. M. a, van Balkom, A. J. L. M., Cath, D. C., van Oppen, P., Uylings, H. B. M., & Veltman, D. J. (2006). Reduced Orbitofrontal-Striatal Activity on a Reversal Learning Task in Obsessive-Compulsive Disorder. Archives of General Psychiatry, 63(11), 1225. https://doi.org/10.1001/archpsyc.63.11.1225

Rouhani, N., Wimmer, G. E., Schneier, F. R., Fyer, A. J., Shohamy, D., & Simpson, H. B. (2019). Impaired generalization of reward but not loss in obsessive-compulsive disorder. Depression and Anxiety, 36(2), 121–129. https://doi.org/10.1002/da.22857

Shen, X., Cox, S. R., Adams, M. J., Howard, D. M., Lawrie, S. M., Ritchie, S. J., Bastin, M. E., Deary, I. J., McIntosh, A. M., & Whalley, H. C. (2018). Resting-State Connectivity and Its Association With Cognitive Performance, Educational Attainment, and Household Income in the UK Biobank. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3(10), 878–886. https://doi.org/10.1016/j.bpsc.2018.06.007

Simmler, L. D., & Ozawa, T. (2019). Neural circuits in goal-directed and habitual behavior: Implications for circuit dysfunction in obsessive-compulsive disorder. Neurochemistry International, 129(April), 104464. https://doi.org/10.1016/j.neuint.2019.104464

Simon, D., Adler, N., Kaufmann, C., & Kathmann, N. (2014). Amygdala hyperactivation during symptom provocation in obsessive-compulsive disorder and its modulation by distraction. NeuroImage: Clinical, 4, 549–557. https://doi.org/10.1016/j.nicl.2014.03.011

Sip, K. E., Gonzalez, R., Taylor, S. F., & Stern, E. R. (2018). Increased Loss Aversion in Unmedicated Patients with Obsessive–Compulsive Disorder. Frontiers in Psychiatry, 8(JAN), 1–10. https://doi.org/10.3389/fpsyt.2017.00309

Stein, D. J., Costa, D. L. C., Lochner, C., Miguel, E. C., Reddy, Y. C. J., Shavitt, R. G., van den Heuvel, O. A., & Simpson, H. B. (2019). Obsessive–compulsive disorder. Nature Reviews Disease Primers, 5(1), 52. https://doi.org/10.1038/s41572-019-0102-3

Stern, E. R., Fitzgerald, K. D., Welsh, R. C., Abelson, J. L., & Taylor, S. F. (2012). Resting-State Functional Connectivity between Fronto-Parietal and Default Mode Networks in Obsessive-Compulsive Disorder. PLoS ONE, 7(5), e36356. https://doi.org/10.1371/journal.pone.0036356

Stern, E. R., Muratore, A. F., Taylor, S. F., Abelson, J. L., Hof, P. R., & Goodman, W. K. (2017). Switching between internally and externally focused attention in obsessive-compulsive disorder: Abnormal visual

cortex activation and connectivity. Psychiatry Research: Neuroimaging, 265(August 2016), 87–97. https://doi.org/10.1016/j.pscychresns.2016.08.006

Stern, E. R., & Taylor, S. F. (2014). Cognitive Neuroscience of Obsessive-Compulsive Disorder. Psychiatric Clinics of North America, 37(3), 337–352. https://doi.org/10.1016/j.psc.2014.05.004

Stern, E. R., Welsh, R. C., Fitzgerald, K. D., Gehring, W. J., Lister, J. J., Himle, J. A., Abelson, J. L., & Taylor, S. F. (2011). Hyperactive Error Responses and Altered Connectivity in Ventromedial and Frontoinsular Cortices in Obsessive-Compulsive Disorder. Biological Psychiatry, 69(6), 583–591. https://doi.org/10.1016/j.biopsych.2010.09.048

Sun, W., & Kober, H. (2020). Regulating Food Craving: From Mechanisms to Interventions. Physiology & Behavior, 112878. https://doi.org/10.1016/j.physbeh.2020.112878

Thorsen, A. L. L., de Wit, S. J. J., de Vries, F. E. E., Cath, D. C. C., Veltman, D. J. J., van der Werf, Y. D. D., Mataix-Cols, D., Hansen, B., Kvale, G., & van den Heuvel, O. A. A. (2019). Emotion Regulation in Obsessive-Compulsive Disorder, Unaffected Siblings, and Unrelated Healthy Control Participants. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4(4), 352–360. https://doi.org/10.1016/j.bpsc.2018.03.007

Tomiyama, H., Nakao, T., Murayama, K., Nemoto, K., Ikari, K., Yamada, S., Kuwano, M., Hasuzawa, S., Togao, O., Hiwatashi, A., & Kanba, S. (2019). Dysfunction between dorsal caudate and salience network associated with impaired cognitive flexibility in obsessive-compulsive disorder: A resting-state fMRI study. NeuroImage: Clinical, 102004. https://doi.org/10.1016/j.nicl.2019.102004

Vaz Serra, A. S., & Abreu, J. L. (1973). Aferição dos quadros clínicos depressivos: ensaio de aplicação do inventário depressivo de Beck a uma amostra portuguesa de doentes deprimidos. Separata de Coimbra Médica, 20, 623–644.

Voon, V., Baek, K., Enander, J., Worbe, Y., Morris, L. S., Harrison, N. A., Robbins, T. W., Rück, C., & Daw, N. (2015). Motivation and value influences in the relative balance of goal-directed and habitual behaviours in obsessive-compulsive disorder. Translational Psychiatry, 5(11), e670–e670. https://doi.org/10.1038/tp.2015.165

Wagner, G., de la Cruz, F., Köhler, S., & Bär, K.-J. (2017). Treatment Associated Changes of Functional Connectivity of Midbrain/Brainstem Nuclei in Major Depressive Disorder. Scientific Reports, 7(1), 8675. https://doi.org/10.1038/s41598-017-09077-5

Xie, C., Ma, L., Jiang, N., Huang, R., Li, L., Gong, L., He, C., Xiao, C., Liu, W., Xu, S., & Zhang, Z. (2017). Imbalanced functional link between reward circuits and the cognitive control system in patients with obsessive-compulsive disorder. Brain Imaging and Behavior, 11(4), 1099–1109. https://doi.org/10.1007/s11682-016-9585-7

Yazici, K. U., & Yazici, I. P. (2019). Decreased theory of mind skills, increased emotion dysregulation and insight levels in adolescents diagnosed with obsessive compulsive disorder. Nordic Journal of Psychiatry, 73(7), 462–469. https://doi.org/10.1080/08039488.2019.1652341

Zilverstand, A., Parvaz, M. A., & Goldstein, R. Z. (2017). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. NeuroImage, 151(8), 105–116. https://doi.org/10.1016/j.neuroimage.2016.06.009

9. Supplementary material

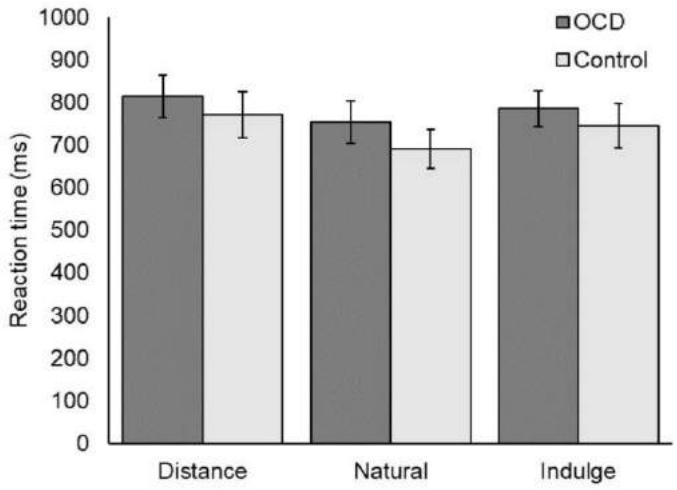


Figure S1 Representation of the reaction time during bidding/food valuation after each cognitive regulation trial (distance, natural, and indulge). No statistically significant differences were found between and within the control and the obsessive-compulsive (OCD) groups. The bars represent the mean and the error bars represent the standard error.

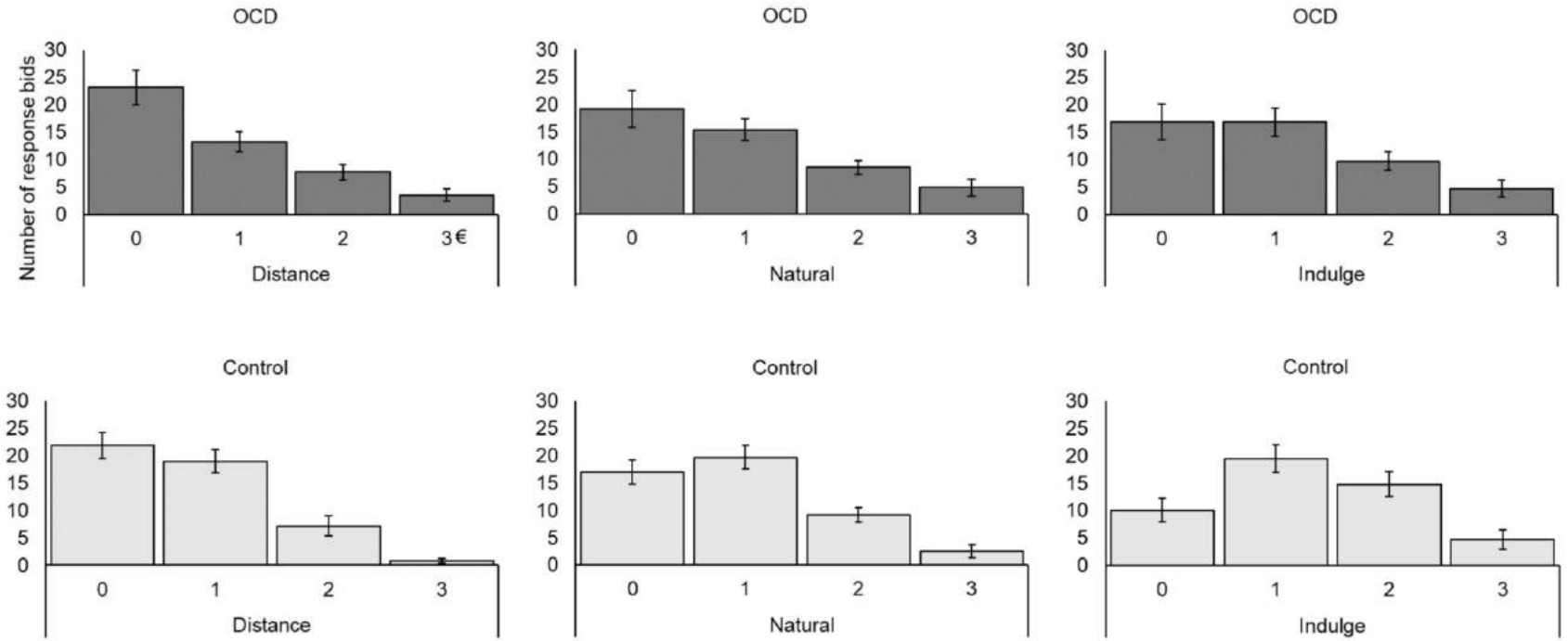


Figure S2 Representation of the number of responses between the control and the obsessive-compulsive (OCD) groups during bidding after each cognitive regulation trial (distance, natural, and indulge). No statistically significant differences were found between and within groups. The bars represent the mean and the error bars represent the standard error.

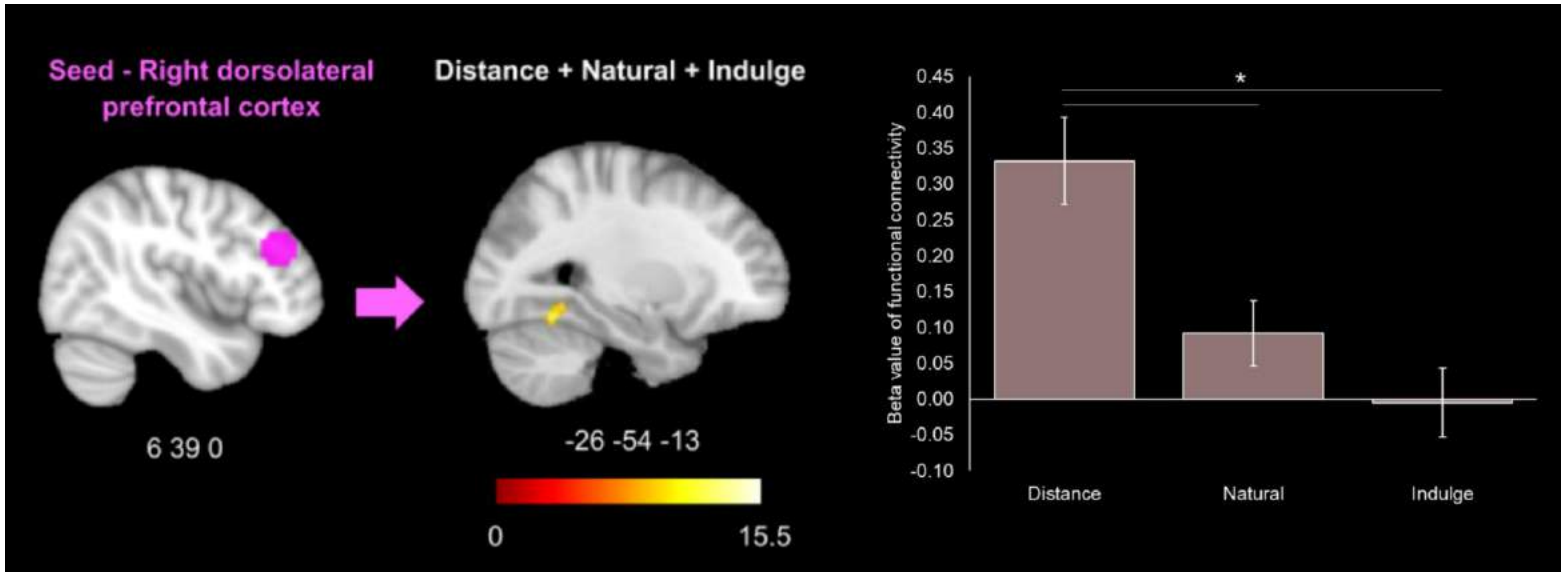


Figure S3 Representation of the main effect of condition (distance, natural, and indulge) during cognitive regulation [$F_{(2, 54)} = 15.4$, $p < 0.001$, $d = 1.5$ [large effect], minimum cluster size 74]. Both groups showed a functional connection between the right dorsolateral prefrontal cortex and a region encompassing the left fusiform gyrus (Brodmann area 37), left occipital lobe (Brodmann area 19), left lingual gyrus, left parahippocampal gyrus, and left cerebellum (posterior lobe) [region with 97 voxels; peak voxel Montreal Neurological Institute coordinates -28, -58, -14]. Post-hoc paired *t*-tests with Bonferroni correction demonstrated that distance trials elicited higher functional connectivity than natural ($t = 3.4$, $p = 0.006$, $d = 0.6$ [medium effect]) and indulge ($t = 5.3$, $p < 0.001$, $d = 1.0$ [large effect]) trials within this region. The colored bar represents the *F*-test values and the Montreal Neurological Institute coordinates are indicated below the brain maps. The graph bars represent the mean values and the error bars the standard error. *Statistically significant results.

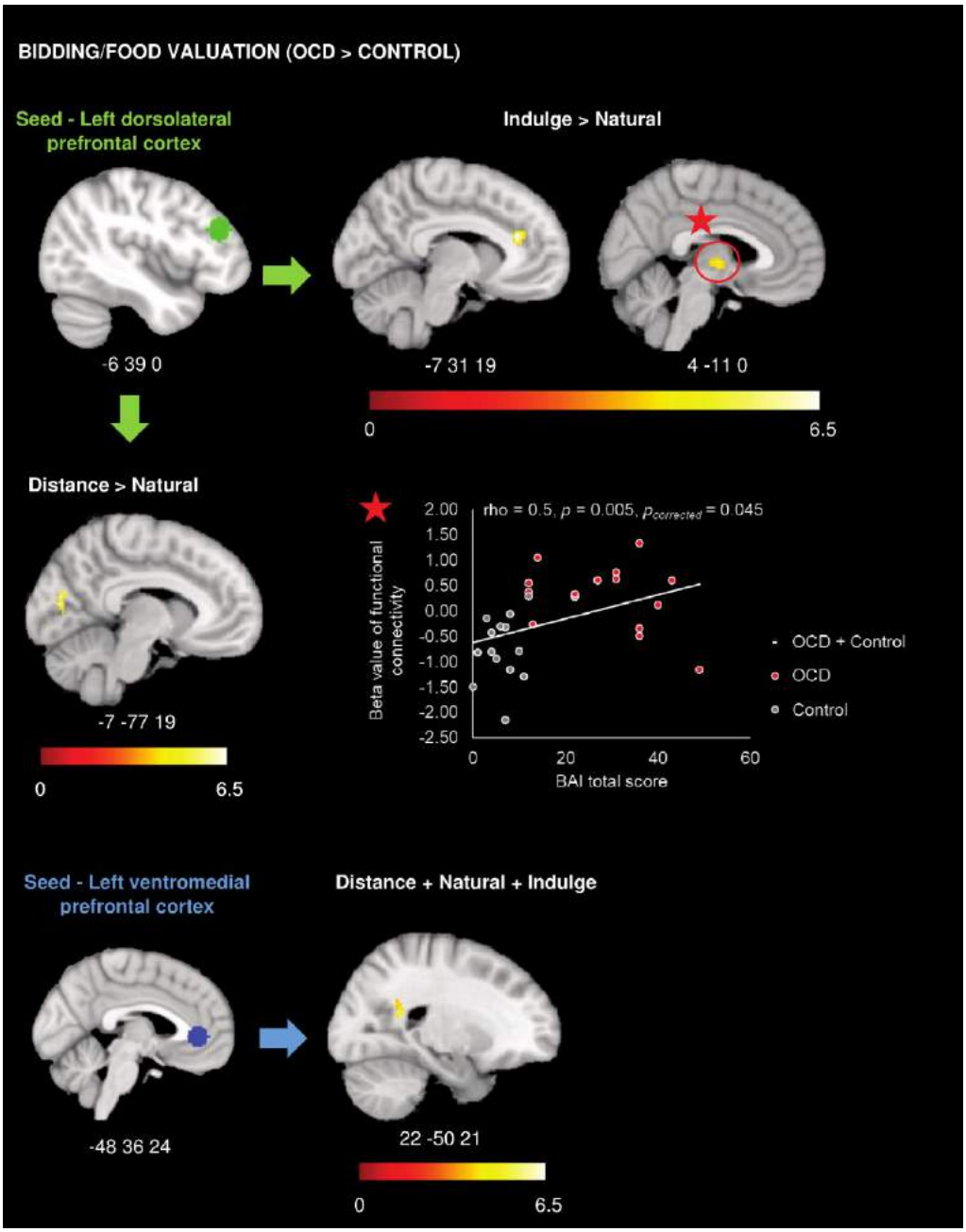


Figure S4 Representation of the functional connectivity differences between groups for food valuation during the task (p<0.001, minimum cluster size 74). The obsessive-compulsive group (OCD) showed increased functional connectivity between the represented regions and the left dorsolateral and ventromedial prefrontal cortices (detailed description in **Table S1**). The colored bar represents the *t*-test or *F*-test values and the Montreal Neurological Institute coordinates are indicated below the brain maps. The graphs indicate statistically significant correlations between functional connectivity values in the regions represented and psychological parameters. BAI - Beck Anxiety Inventory.

Table S1 Regions with differential functional connectivity between the control and obsessive-compulsive disorder groups during bidding/valuation, using the ventromedial and dorsolateral prefrontal cortical seeds ($p < 0.001$, minimum cluster size of 74 voxels).

Brain regions	Cluster size (voxels)	MNI peak voxel coordinates	Peak voxel intensity	Cohen's *d* effect size
Seed - L dlPFC				
OCD > control				
Distance > Natural				
L, R Cuneus, L, R Calcarine (BA 17), R Precuneus, R superior occipital gyrus (BA 18), R Parietal lobe, R Posterior cingulate gyrus (BA 23 and 31)	78	-8 -80 12	$t_{(18)} = 6.3$	$d = 2.3$ (large)
Indulge > Natural				
R Thalamus (medial dorsal nucleus)	79	2 -6 0	$t_{(18)} = 5.3$	$d = 2.0$ (large)
L Anterior cingulate cortex (BA 24 and 32), L Middle/superior frontal gyrus (BA 9 and 10), L Superior medial frontal gyrus,	144	-8 32 20	$t_{(18)} = 6.4$	$d = 2.4$ (large)
Seed - L vmPFC				
OCD > control				
Distance + Natural + Indulge (group main effect)				
R Temporal lobe (BA 41), R Transverse temporal gyrus, R Precuneus, R Parietal lobe, R Posterior cingulate gyrus	97	24 -50 20	$F_{(2, 54)} = 6.3$	$d = 1.0$ (large)

MNI - Montreal Neurologic Institute; L - Left; R - Right; dlPFC - dorsolateral prefrontal cortex; vmPFC - ventromedial prefrontal cortex; OCD – obsessive-compulsive disorder; BA – Brodmann area.

CHAPTER V

The efficacy of biofeedback approaches for obsessive-compulsive and related disorders: a systematic review and meta-analysis

Sónia Ferreira, José Miguel Pêgo, Pedro Morgado

Article published in Psychiatry Research, 18 Dec 2018

DOI: 10.1016/j.psychres.2018.12.096

Link: https://www.sciencedirect.com/science/article/abs/pii/S0165178118316391?via%3Dihub

Psychiatry Research 272 (2019) 237–245

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Review article

The efficacy of biofeedback approaches for obsessive-compulsive and related disorders: A systematic review and meta-analysis

Sónia Ferreira[a,b], José Miguel Pêgo[a,b], Pedro Morgado[a,b,*]

[a] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal
[b] ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal

ARTICLE INFO

Keywords:
Neurofeedback
Obsessive-compulsive disorder
Self-regulation
Treatment outcome
Functional magnetic resonance imaging
Electroencephalography
Human

ABSTRACT

Biofeedback is applied to target excessive and/or deficient physiological signals to help patients identifying and self-managing their symptoms. Biofeedback has been employed in psychiatric disorders, including obsessive-compulsive disorder (OCD), mainly by using neural signals - neurofeedback. Recently, OCD has been integrated into the obsessive-compulsive and related disorders (OCD&RD) category (body dysmorphic, hoarding, trichotillomania/hair-pulling, and excoriation/skin-picking disorders). The efficacy of biofeedback for OCD&RD is still unknown. Our work provides a complete overview of publications assessing the therapeutic efficacy of biofeedback in OCD&RD with a systematic review and meta-analysis. We found ten studies involving 102 OCD participants (three randomized controlled trials) mostly applying neurofeedback (one publication used thermal biofeedback). Five neurofeedback studies were selected for meta-analysis (89 patients; two randomized controlled trials). The overall effect size within the treatment group varied between medium to large, but high heterogeneity and inconsistency values were found. The methodological quality was low indicating a high risk of bias. In conclusion, a beneficial effect of neurofeedback for OCD patients was found but also critical limitations on methodology, high heterogeneity among studies, and a putative reporting bias. Future research following high-quality guidelines should be conducted to address the efficacy of biofeedback approaches for OCD&RD.

1. Introduction

OCD is the fourth most common psychiatric disorder and the tenth cause of disability worldwide. OCD is characterized by recurrent thoughts (obsessions) associated with high anxiety, followed by repetitive behaviors or mental tasks to relieve the anxiety (compulsions) (Rapp et al., 2016; Sachs and Erfurth, 2018). Anxiety symptoms comprise autonomic nervous system dysregulation namely increased heart rate, decreased heart rate variability, elevated skin electrodermal activity, and augmented breathing rate (Schoenberg and David, 2014; Simon et al., 2013). OCD is also characterized by a hyperactive orbitofronto-striatal circuit including the orbitofrontal and cingulate cortices and subcortical structures (basal ganglia, hippocampus, and amygdala) (Bruin et al., 2018; Moreira et al., 2017). Recently, OCD has been integrated into the OCD&RD category in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This category includes OCD, body dysmorphic disorder, hoarding disorder, trichotillomania/hair-pulling disorder, excoriation/skin-picking disorder, substance/medication-induced OCD&RD, and OCD&RD induced by other medical condition. These disorders share compulsive behaviors, impaired behavioral inhibition, demographic characteristics (onset age, family patterns, and comorbidity), neural pathways (e.g. increased basal ganglia activity) and neurotransmitter dysfunction (serotonergic and dopaminergic systems imbalance), and treatment response profiles (Abramowitz, 2018; American Psychiatric Association, 2013).

First-line treatments include cognitive-behavioral therapy (CBT) and antidepressants. However, up to 60% of patients do not present symptomatic remission after treatment (Seibell and Hollander, 2014). The limited success of conventional treatments makes identifying alternative therapies a priority. Self-regulation is the ability to manage emotions, thoughts, or behaviors in face of specific stimuli

Abbreviations: OCD, obsessive-compulsive disorder; OCD&RD, obsessive-compulsive and related disorders; CBT, cognitive-behavioral therapy; DSM-5, fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; PI-WSUR, Padua Inventory–Washington State University Revision

* Corresponding author at: Escola de Medicina, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal.
E-mail addresses: id6533@alunos.uminho.pt (S. Ferreira), jmpego@med.uminho.pt (J.M. Pêgo), pedromorgado@med.uminho.pt (P. Morgado).

https://doi.org/10.1016/j.psychres.2018.12.096
Received 7 September 2018; Received in revised form 8 December 2018; Accepted 18 December 2018
Available online 20 December 2018
0165-1781/ © 2018 Elsevier B.V. All rights reserved.

(Pearcy et al., 2016). Biofeedback is a technique aiming to inhibit excessive and/or reinforce impaired physiological signals to help patients in identifying and managing their symptoms. It is also applied to improve the performance or cognitive skills. Usually, biosignal changes are measured and presented to patients in form of auditory or visual feedback so they can learn how to self-regulate their biological responses. These signals might be related to heart rate, skin conductance, temperature levels, respiratory pattern, or muscle activity (Schoenberg and David, 2014).

Biofeedback has been applied to psychiatric disorders such as anxiety, depression, and schizophrenia with a specific type of feedback from neural activity in target brain regions – neurofeedback (Schoenberg and David, 2014; Sitaram et al., 2016). The neurofeedback technique is mostly implemented with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) (Begemann et al., 2016; Sitaram et al., 2016; Thibault et al., 2018).

Previous authors have explored the efficacy of biofeedback (Schoenberg and David, 2014) and neurofeedback (Begemann et al., 2016; Gonçalves et al., 2017; Micoulaud-Franchi et al., 2015) in psychiatric disorders, including OCD. These works described that EEG neurofeedback reduces OCD rumination and anxiety (Schoenberg and David, 2014) and has a superior effect compared to sham neurofeedback (false feedback signal used as a placebo condition) (Micoulaud-Franchi et al., 2015). Moreover, EEG neurofeedback effects were reported to be similar to medication, mainly for reducing compulsions (Begemann et al., 2016). Lastly, OCD patients learned how to regulate brain regions (the anterior insula and orbitofrontal cortex) with fMRI neurofeedback leading to clinical improvement (Gonçalves et al., 2017).

However, the efficacy of biofeedback techniques for the OCD&RD is still unknown. Prior studies have mainly focused on neurofeedback approaches and OCD. It is important to explore the literature to establish adequate biofeedback protocols to maximize the clinical outcomes for patients. This work aims to review the evidence for the therapeutic efficacy of biofeedback in OCD&RD. Our work provides qualitative and quantitative information to evaluate if biofeedback is a viable therapeutic approach for OCD&RD.

2. Methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) norms (Liberati et al., 2009; Moher et al., 2009). The study protocol was not registered at PROSPERO (Centre for Reviews and Dissemination, York, U. K., https://www.crd.york.ac.uk/prospero).

2.1. Eligibility criteria

All studies regarding the efficacy of biofeedback techniques in the reduction of symptomatic manifestation in OCD&RD were considered. Only studies conducted with humans, published in English, and reporting original results were selected (conference abstracts, reviews, and book chapters were excluded).

2.2. Information sources

Studies were identified by searching electronic databases and reference lists of articles. This search was last conducted on 27th of August 2018 in Medline, Web of Science, Scopus, and PsycINFO without any date restrictions. The search was conducted by the author SF.

2.3. Search

The following setup of search terms was used for Medline and similar terms were used for the other databases: ("obsessive-compulsive disorder" OR "body dysmorphic disorders" OR "hoarding disorder" OR "trichotillomania" OR "hair-pulling disorder" OR "excoriation disorder" OR "skin-picking disorder") AND ("neurofeedback" OR "biofeedback").

2.4. Study selection

Eligibility assessment was performed by the author SF. In case of doubt, the results were discussed among all authors. All trials were included, regardless of the existence and type of a comparator group. The primary outcome measure was the effect of biofeedback on symptomatic manifestation based on psychometric scales. Articles including participants with obsessive-compulsive tendencies or symptoms without a diagnosis were excluded. Moreover, studies with several disorders including OCD&RD that did not present the results for each condition individually were also excluded. Articles that did not use biofeedback as a therapeutic approach were also excluded. Works not assessing symptomatic changes after biofeedback application were also excluded.

2.5. Data collection process

We develop a data extraction sheet based on a previous review article (Schoenberg and David, 2014) and refined it to simplify the organization of information. All data extracted by the author SF was confirmed twice to avoid errors. In case of doubt, the results were discussed among all authors. Studies from the same research group or group of authors were carefully analyzed to avoid double counting the same data.

2.6. Data items

From each study, we extracted the following data items: (1) participant groups [sample size, average age, and gender ratio]; (2) disorder [type, method of diagnosis, previous/current treatment approaches, and associated comorbidities]; (3) biofeedback intervention [type of biosignal, number of sessions, session duration, and outcome measures].

2.7. Risk of bias in individual studies

To ascertain the risk of bias of the eligible studies, the author SF determined the quality of each study concerning study control, randomization, patients' blindness, researchers' blindness, and sponsoring bias. Three levels were used for evaluating each parameter: low, moderate, and high quality (Higgins and Green, 2008; Liberati et al., 2009).

2.8. Synthesis of results

For each study, the mean score and standard deviation of psychometric scales at baseline and after biofeedback intervention were extracted or calculated from median values (Hozo et al., 2005) or individual data. Only scales reflecting the severity of symptoms were considered. The effect size of the intervention was determined based on the standardized mean change. Since individual data was not available in most of the studies, we considered a correlation coefficient (r) of 0.6 between pre and post-intervention measures (Morris, 2008; Morris and DeShon, 2002; Nakagawa and Cuthill, 2007) [the supplementary Figure S.1 and Figure S.2 represent the main results for a lower $r = 0.1$ and higher $r = 0.9$, respectively]. Studies reporting only qualitative results, insufficient data for the effect size calculation, and low sample sizes preventing statistical analysis ($n < 3$ per group) were excluded.

Heterogeneity (Cochrane's Q) and inconsistency (I^2) values were also calculated (Hardy and Thompson, 1998; Higgins, 2003; Higgins and Thompson, 2002). Ninety-five percent confidence intervals (CI) were considered. All calculations and graphs were executed in R version

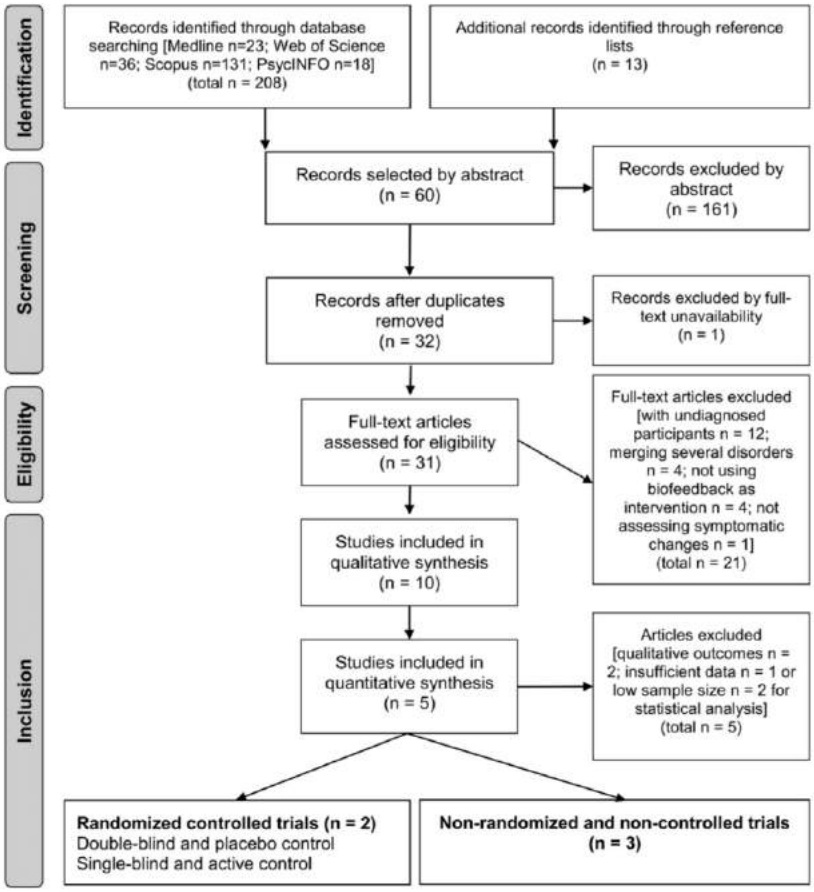


Fig. 1. Flow diagram of the literature search [adapted from (Liberati et al., 2009; Moher et al., 2009)].

3.4.3 (package "metaphor", The R Foundation, https://www.r-project.org/) using a random effects model.

2.9. Risk of bias across studies

To assess bias across studies, a funnel plot was constructed. Given the small number of studies included for meta-analysis (Fig. 1), the Egger's test was not performed to evaluated funnel plot asymmetry (Sterne et al., 2011), thus, asymmetry was visually inspected.

2.10. Additional analyses

To evaluate if the effect size heterogeneity was explained by the patients' characteristics in each study, an exploratory meta-regression was performed using the mean age and gender ratio (females/males proportion) as predictors (Table 1). Additionally, the mean number of biofeedback sessions was also introduced as a predictor to analyze if the effect size depended on treatment duration (session duration information was not available for all studies, preventing the calculation of treatment duration in time; Table 2) (Thompson and Higgins, 2002).

3. Results

3.1. Study selection

Fig. 1 shows the flow diagram representative of the process of studies selection. A total of 221 studies were identified through databases searching (n = 208) and by checking relevant articles in reference lists (n = 13). No unpublished articles were found. From those, 32 studies were selected to be included in the review after reading the abstract and removing duplicates. From those, 1 study was discarded because the full text was not available even after contacting the authors. The remaining 31 articles were examined in detail. Twenty-one studies did not meet the inclusion criteria: studies including participants without a diagnosis of OCD&RD (n = 12), studies presenting results for a group merging several disorders including OCD&RD (n = 4), articles not using the biofeedback technique as a therapeutic intervention (n = 4), and studies not assessing symptomatic changes associated with OCD&RD (n = 1).

3.2. Study characteristics

All studies included in the systematic review (n = 10) involved OCD patients and were published between 1974 and 2015. Two multicentric studies were conducted in Germany, Italy, USA, and Chile (Buyukturkoglu et al., 2015), and the Czech Republic and France

Table 1
Summary of demographic and clinical information of the studies included for systematic reviewing.

Study	Group	Sample size	Gender (F | M)	Mean age (years)	OCD diagnosis	Comorbidities	Other treatment (Psychotherapy | Medication)
Mills and Solyom, 1974	Treatment	5	3 | 2	32.1	–	Depression (n = 1); death phobia (n = 1)	4 | 4
LeVine et al., 1983	Treatment	1	1 | 0	30s	DSM-III	Muscle palsy (n = 1)	1 | 1
Hammond, 2003	Treatment	2	1 | 1	25.0	–	Depression (n = 2); insomnia (n = 1); attention deficit disorder (n = 1); attention deficit hyperactivity disorder (n = 1); substance abuse (n = 1)	0 | 2
Hammond, 2004	Treatment	1	0 | 1	23.0	–	Depression (n = 1)	0 | 1
Sürmeli and Ertem, 2011	Treatment	36	24 | 12	30.1	DSM-IV	None	0 | 36
Barzegary et al., 2011	Treatment	4	2 | 2	28.2	DSM-IV	None	–
	Control 1	4	2 | 2	31.7			
	Control 2	4	2 | 2	28.2			
Koprivová et al., 2013	Treatment	8	7 | 1	27.5	DSM-IV; ICD-10	None	0 | 6
	Control	10	7 | 3	28.5			0 | 7
Scheinost et al., 2014	Treatment	5	2 | 3	45.6	–	Major depressive disorder (n = 3); panic disorder with agoraphobia (n = 1); generalized anxiety disorder (n = 1); substance abuse (n = 1); body dysmorphic disorder (n = 1); motor tic (n = 1)	0 | 1
Deng et al., 2014	Treatment	37	19 | 21[a]	26.7[a]	ICD-10	None	0 | 11[a]
	Control	35	19 | 20[b]	26.6[b]			0 | 9[b]
Buyukturkoglu et al., 2015	Treatment	3	2 | 1	23.3	DSM-IV (SCID-I)	Depression (n = 2)	2 | 2

[a] Including 3 dropout patients;
[b] Including 4 dropout patients; OCD = Obsessive-compulsive disorder; F = Female; M = Male; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Statistical Classification of Diseases and Related Health Problems; SCID = Structured Clinical Interview.

Table 2
Summary of the biofeedback intervention information of the studies included for systematic reviewing and meta-analysis.

Study	Group	Biofeedback intervention	Biosignal	Mean number of sessions	Session duration (min)	Outcome measure	Effect size within treatment group [CI 95%]
Mills and Solyom, 1974	Treatment	EEG	EEG alpha at O1 and O2 (8–13 Hz; > 20 μv)	15.2	60	–	Qualitative outcomes
LeVine et al., 1983	Treatment	Thermal	Hand fingers temperature	–	30	–	Qualitative outcomes
Hammond, 2003	Treatment	qEEG	Individualized EEG	71.5	15–35	Y-BOCS	Low sample size
Hammond, 2004	Treatment	qEEG	Individualized EEG	43.0	30	Y-BOCS	Low sample size
Sürmeli and Ertem, 2011[a]	Treatment	qEEG	Individualized EEG	50.2	60	Y-BOCS	2.18 [1.60; 2.77]
Barzegary et al., 2011	Treatment	qEEG	Individualized EEG	30.0	45	PI-WSUR	Insufficient data
	Control 1	Drug	–	–	–		
	Control 2	No treatment	–	–	–		
Koprivová et al., 2013[a]	Treatment	EEG + CBT	Individualized EEG	25.0	30	Y-BOCS	1.02 [0.28; 1.75]
	Control	EEG sham + CBT					
Scheinost et al., 2014[a]	Treatment	fMRI	BOLD from orbitofrontal/ BA 10	1.6	–	Y-BOCS	3.31 [1.23; 5.40]
Deng et al., 2014[a]	Treatment	EEG + Drug + CBT	EEG alpha, sensorimotor rhythm, and theta	40.0	24	Y-BOCS	6.23 [4.80; 7.66]
	Control	Drug + CBT	–	–	–		
Buyukturkoglu et al., 2015[a]	Treatment	fMRI	BOLD from anterior insula	10.0	–	Y-BOCS	0.01 [−0.64; 0.66]

EEG = Electroencephalography; qEEG = quantitative electroencephalography guided electroencephalography biofeedback; CBT = Cognitive-behavioral therapy; fMRI = functional magnetic resonance imaging; O1 = left occipital; O2 = right occipital; BOLD = Blood-oxygen-level dependent; BA = Brodmann area; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; PI-WSUR = Padua Inventory–Washington State University Revision; CI = Confidence interval.
[a] studies included meta-analysis.

(Koprivová et al., 2013). The other works were performed in Turkey (Sürmeli and Ertem, 2011), Iran (Barzegary et al., 2011), Canada (Mills and Solyom, 1974), China (Deng et al., 2014), and USA (Hammond, 2004, 2003; LeVine, 1983; Scheinost et al., 2014). Three works were randomized controlled trials (Barzegary et al., 2011; Deng et al., 2014; Koprivová et al., 2013). From these 3 trials, 1 was a double-blind study (Koprivová et al., 2013) and 1 was a single-blind study (Deng et al., 2014). The remaining studies were not controlled.

Table 1 shows a summary of the studies included in the systematic review. The total number of OCD patients enrolled in the biofeedback intervention was 102 and 53 OCD patients were included in control groups. The average age of the treated patients was 29.1 (6.9) years [mean (standard deviation)] and for the control patients was 28.7 (2.1) years. The biofeedback intervention group had a total of 61 females and 44 males [including a study with 3 dropout patients (Deng et al., 2014)] and the control group had 30 females and 27 males [including a study with 4 dropout patients (Deng et al., 2014)].

All studies applied an intervention based on neurofeedback with fMRI ($n = 2$ (Buyukturkoglu et al., 2015; Scheinost et al., 2014)) or EEG ($n = 7$), except one publication that used thermal biofeedback (LeVine, 1983). Two studies combined the neurofeedback effects with CBT (Koprivová et al., 2013) or medication and CBT (Deng et al., 2014). For control, the 3 trials mentioned above used a waiting list group and medication group (Barzegary et al., 2011), a medication and CBT combined group (Deng et al., 2014), or a sham biofeedback and CBT combined group (Koprivová et al., 2013). The biofeedback intervention had an average duration of 31.8 (21.8) sessions (one study with missing information (LeVine, 1983)). The brain regions target during the neurofeedback intervention were the anterior insula (Buyukturkoglu et al., 2015) and orbitofrontal cortex/Brodmann area 10 (Scheinost et al., 2014), but most of the studies used an individualized approach targeting subject-specific brain regions with abnormal activation (Barzegary et al., 2011; Hammond, 2003, 2004; Koprivová et al., 2013; Sürmeli and Ertem, 2011). The studies selected for the systematic review did not include overlap data from the same participant. Table 2 shows a summary of the intervention characteristics of the studies included in the systematic review.

The main outcome measure was the change in psychometric scales score associated with symptomatic manifestation. Results are presented for the Y-BOCS ($n = 7$) or Padua Inventory–Washington State University Revision (PI-WSUR; $n = 1$ (Rapp et al., 2016)) since both scales evaluate the severity of obsessive-compulsive symptoms (Table 2). Psychometric scales assessing other parameters (e.g. depression and anxiety) were used only once per study, thus, were excluded from the analysis. Two studies were excluded from the meta-analysis because they reported only qualitative outcomes (LeVine, 1983; Mills and Solyom, 1974). Additionally, 2 publications with small sample sizes ($n = 1$ (Hammond, 2004) and $n = 2$ (Hammond, 2003)) were not included because the effect size could not be estimated. We also excluded another study due to the lack of information for statistical calculation (Barzegary et al., 2011) after contacting the authors without success. In conclusion, 10 studies were accepted for the systematic review and 5 for the meta-analysis.

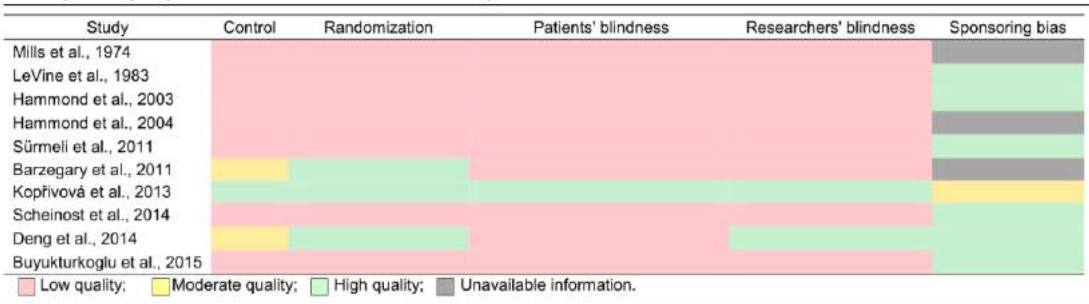
3.3. Risk of bias within studies

Table 3 indicates the information regarding the quality of the studies included in the systematic review. Most of the works presented low quality for the evaluated parameters, except for sponsoring bias. Only the 3 controlled and randomized trials were considered moderate to high-quality publications (Barzegary et al., 2011; Deng et al., 2014; Koprivová et al., 2013). Nonetheless, 2 studies did not control for placebo effects (Barzegary et al., 2011; Deng et al., 2014). The third one was sponsored by a company and lacked a conflict of interests statement, thus, we considered only moderate quality regarding sponsoring bias (Koprivová et al., 2013).

3.4. Results of individual studies

All 5 studies considered for meta-analysis applied a neurofeedback intervention with OCD patients and used the Y-BOCS scale to measure symptomatic changes. Taking into account that only 2 (Deng et al., 2014; Koprivová et al., 2013) of the 5 studies selected were controlled and that distinct control groups were used, the effect size estimation was only performed within the intervention group - the standardized mean change of Y-BOCS scores from baseline to after neurofeedback (Table 2). Effect size calculation is represented in Table 2 and on the forest plot in Fig. 2. The within-group effect of neurofeedback treatment for OCD patients varied from small to large values for individual studies (McGrath and Meyer, 2006; Tomczak and Tomczak, 2014).

Table 3
Summary of the quality assessment of the studies included in the systematic review.



3.5. Synthesis of results

The overall within-group effect size was 2.47 (CI 95% 0.37; 4.57), a large effect size favoring the neurofeedback intervention for OCD patients (McGrath and Meyer, 2006; Tomczak and Tomczak, 2014). However, the CI pointed to a large standard error for this effect size. Moreover, the meta-analysis revealed a high heterogeneity value [Q (df = 4) = 71.59, $p < 0.0001$] corresponding to an elevated value of inconsistency (I^2) of 96.64% (CI 95% 90.01%; 99.60%) [Fig. 2].

3.6. Risk of bias across studies

The funnel plot in Fig. 3 indicates strong data asymmetry, possibly reflecting the existence of reporting bias, poor methodological designs, and the high heterogeneity values reported above (Sterne et al., 2011).

3.7. Additional analyses

Results from the exploratory meta-regression indicated that the heterogeneity values [Q residual (df = 1) = 37.35, $p < 0.0001$; Q predictors (df = 3) = 0.90, p = 0.82; I^2 = 97.32% (CI 95% 86.55%; > 99.73%] were not explained by the predictors. The average age [B = 0.09; Z = 0.37; p = 0.72], gender ratio [B = −0.40; Z = −0.55; p = 0.58], and mean session duration [B = 0.06; Z = 0.63; p = 0.53] did not present a statistically significant effect on the model.

4. Discussion

Our work aimed to evaluate the evidence for therapeutic efficacy of biofeedback in OCD&RD, albeit all publications selected pertain to OCD patients and mostly neurofeedback interventions. The results point to a positive effect of neurofeedback in OCD patients' symptomology but reveal serious limitations on the research procedures (e.g. lack of proper control groups and small sample sizes), high heterogeneity among studies, and a putative reporting bias. To conclude, further research with high-quality standards is needed to address the efficacy of neurofeedback in OCD. Additionally, biofeedback should be explored as a potential therapy for other OCD&RD.

Body dysmorphic disorder, hoarding disorder, trichotillomania/hair-pulling disorder, and excoriation/skin-picking disorder are related OCD diseases that may also benefit from biofeedback approaches (Abramowitz, 2018; Sachs and Erfurth, 2018), thus, more studies should be performed in the future. Additionally, other biofeedback interventions apart from neurofeedback (e.g. approaches using skin conductance, respiratory, or electrocardiogram signals) might have the potential to be used in ecological environments at lower costs (Schoenberg and David, 2014). Indeed, devices incorporating mobile technology are starting to be applied to help patients with psychiatric disorders in everyday life (Adams et al., 2017; Bhugra et al., 2017; Loo Gee et al., 2016; Van Ameringen et al., 2017; Versluis et al., 2016). Nonetheless, EEG neurofeedback is also a widely available technique that lacks the regional resolution of fMRI, especially for activity in deep/subcortical areas, but implicates lower costs and good temporal

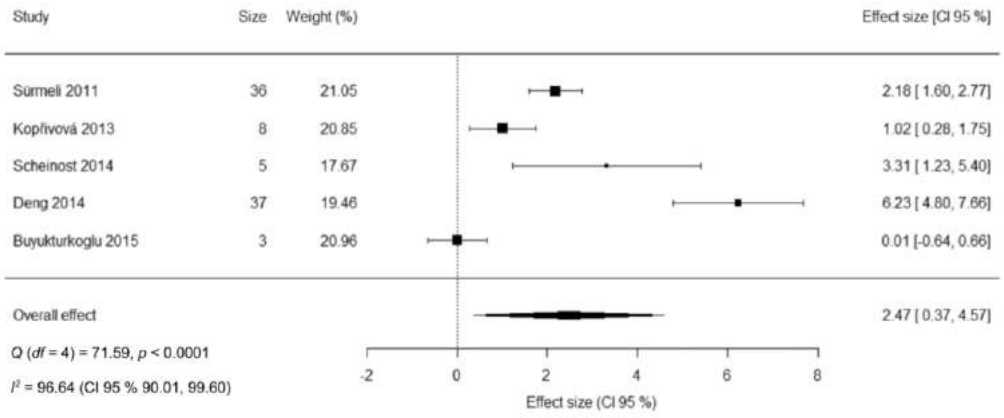


Fig. 2. Forest plot representing the meta-analysis results of neurofeedback treatment for obsessive-compulsive patients' symptoms. The Yale-Brown Obsessive Compulsive Scale score was used as outcome measure within the treatment group. Studies' citation lack "et al." for better visualization purpose. CI = Confidence interval; Q = Heterogeneity; I^2 = Inconsistency.

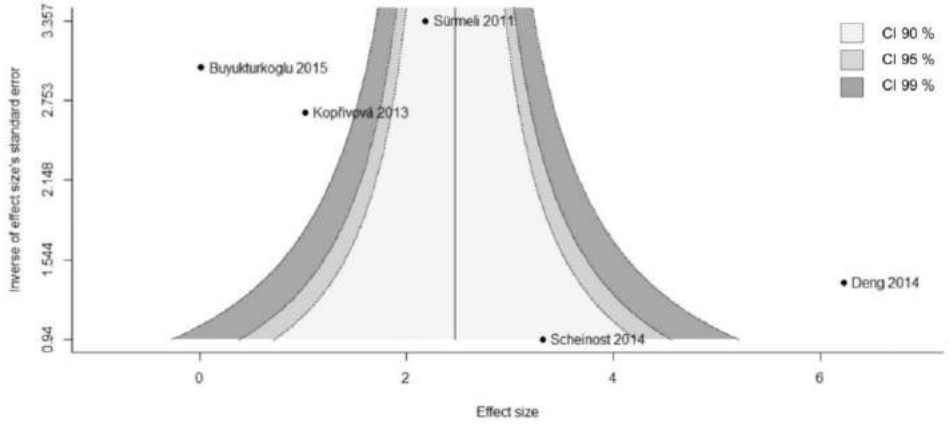


Fig. 3. Funnel plot representing considerable asymmetry in meta-analysis results of neurofeedback treatment for obsessive-compulsive patients' symptoms. The Yale-Brown Obssessive Compulsive Scale score was used as outcome measure within the treatment group. Studies' citation lack "et al." for better visualization purpose. CI = Confidence interval.

resolution. fMRI has a better spatial resolution to localize brain regions but has low temporal resolution and entails high costs (Begemann et al., 2016; Sitaram et al., 2016; Thibault et al., 2018) .

Studies included merely for the systematic review presented a reduction in OCD symptoms after neurofeedback (Barzegary et al., 2011; Hammond, 2004, 2003; LeVine, 1983; Mills and Solyom, 1974). Regarding the meta-analysis results, the overall effect of neurofeedback in the symptomatology of OCD patients was high. However, this value concerns only changes in the intervention group (within-group analysis). Only two studies from the meta-analysis were controlled (Deng et al., 2014; Koprivová et al., 2013) and the type of control group was distinct, preventing a conclusive between-group analysis on the effect size. Nonetheless, these two trials were included in a previous review (Begemann et al., 2016) regarding EEG neurofeedback effects in psychiatric diseases, where authors reported a moderate to high between-group effect mainly for compulsive symptoms. However, Kopřivová et al. (2013) was the only study accounting for placebo effects by using a sham neurofeedback control group. Since patients are always aware of the neurofeedback intervention, it is crucial to have placebo (Arns et al., 2017; Rogala et al., 2016; Sitaram et al., 2016) or/and active controlled studies. Indeed, some reports point that active comparators such as medication or CBT might be better than sham groups because psychiatric treatments usually involve a placebo component that might positively affect the outcomes (Geddes and Cipriani, 2015; Hammond, 2011; Pigott et al., 2018).

Another drawback of the selected studies was the small sample size. For the meta-analysis, the sample size ranged from 3 to 37 patients with more than half of the studies including less than 10 patients. Additionally, more women than men were included (54 women versus 38 men). Previous research indicated that OCD male patients show a higher vulnerability for more severe disease manifestation (Goldberg et al., 2015). Moreover, OCD is a very heterogeneous disease with different symptomatic dimensions (contamination/cleaning, symmetry/repeating/ordering/counting, sexual/religious/aggressive, and harming) (American Psychiatric Association, 2013). Thus, patients might respond differently to biofeedback interventions depending on obsession and compulsion categories (Thorsen et al., 2018) and gender. Some of the studies included in our review lack information about symptomatic dimensions of patients and the diagnosis instruments. Future studies should provide clear information about patients' diagnosis and symptoms to better characterize biofeedback outcomes. Furthermore, more than half of the studies included OCD patients with comorbidities which may have an influence on intervention outcomes. All these factors might have contributed to the high level of heterogeneity among studies. Lastly, the selected studies lack clear information regarding the proportion of responder patients based on specific criteria (except (Deng et al., 2014)) and secondary effects of neurofeedback. Moreover, the heterogeneity may also arise from the inclusion of studies with different neurofeedback modalities (fMRI and EEG) and distinct target brain regions. More studies were performed with fMRI than EEG feedback possibly because fMRI is a less available, less practical, newer, and more expensive technique. Indeed, the two studies using fMRI neurofeedback have a low sample size possibly indicating that these were pilot works.

The reported effect size was not associated with the number of neurofeedback sessions and the sample characteristics (age and gender ratio). This conclusion must be interpreted with caution given the small number of studies included in the meta-regression and that the number of sessions may be a biased measure of the intervention duration (these results may be false negatives). Unfortunately, not all the studies reported session duration values, preventing a real estimation of the intervention length. Future publications should clearly describe the intervention protocol to allow replication.

In clinical terms, neurofeedback might have the potential for treatment-resistant patients to minimize prolonged treatment periods and the use of invasive therapies such as deep brain stimulation and radiosurgery (Micoulaud-Franchi et al., 2015; Seibell and Hollander, 2014). Additionally, EEG portable systems and mobile devices are being developed to allow a more ecological biofeedback approach in the future (Enriquez-Geppert et al., 2017). Indeed, recent findings with OCD and Tourette Syndrome patients suggest that fMRI neurofeedback leads to a continuous symptomatic improvement even weeks after the end of the intervention. Thus, more ecological techniques might imply longer biofeedback effects. These authors claim that patients might adopt the skills learned during neurofeedback in a similar way to CBT (Rance et al., 2018). A recent meta-analysis addressing the therapeutic effect of CBT in OCD symptoms revealed a medium to large effect size (Carpenter et al., 2018). However, this work was conducted with four randomized placebo-controlled trials, thus, results cannot be compared to ours. Another meta-analysis (Sugarman et al., 2017) of thirteen trials evaluating the therapeutic outcomes of several antidepressant drugs for OCD also reported a medium to a large effect size of the medication without considering the placebo control. Although our review shows a similar effect size, the included studies have patients already exposed to medication and, some of them, psychotherapy. Despite the implementation of washout periods before neurofeedback in some

publications, the use of other treatment approaches might have influenced the results. Future works should consider previous/current treatments as a potential confounding variable.

4.1. Limitations

The search methodology was performed by a sole author (SF), although a strict procedure was followed accordingly to PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009).

We included non-randomized and non-controlled studies to provide a complete and clinically helpful overview of biofeedback interventions for OCD&RD. This process enabled us to highlight flaws and novel research approaches for future works.

Our results may have been influenced by publication bias. Our search was limited by articles published in English and one publication was not available for full-text reading. No unpublished studies were found, but our search was limited to four databases. Nonetheless, the analysis of reference lists allowed a more exhaustive search. Additionally, three publications were not selected for meta-analysis due to incomplete or qualitative reporting of outcomes possibly increasing reporting bias (Barzegary et al., 2011; LeVine, 1983; Mills and Solyom, 1974). Lastly, the new categorization of OCD&RD in DSM-5 might prevent the retrieval of articles following the last classification. However, our search was conducted with specific disorder names to avoid missing information.

4.2. Conclusions

In summary, the poor methodological quality of the select studies prevents evidence-based conclusions on the efficacy of neurofeedback in the treatment of OCD. Moreover, the lack of studies addressing other biofeedback interventions and OCD related disorders highlights the need for further research. Thus, CBT and drug therapy remain at the forefront of OCD&RD treatment.

Future studies should follow high-quality guidelines namely predetermined sample sizes (with power calculation), randomization and blinding, selection of proper control groups, a complete clinical characterization of patients, and a clear description of biofeedback protocols and study outcomes.

Declarations of interest

None.

Acknowledgments

We would like to thank Pedro Moreira for the help with the statistical analysis.

Funding

This work has been funded by FEDER funds, through the Competitiveness Factors Operational Programme (COMPETE), and by National funds, through the Foundation for Science and Technology (FCT), under the scope of the project POCI-01-0145-FEDER-007038. This article has been developed under the scope of the project NORTE-01-0145-FEDER-000013, supported by the Northern Portugal Regional Operational Programme(NORTE 2020), under the Portugal 2020 Partnership Agreement, through the European Regional Development Fund (FEDER), and the BIAL foundation, Porto, Portugal (grant number PT/FB/BL-2016-206). SF was supported by a combined Ph. D. scholarship from FCT and the company iCognitus4ALL - IT Solutions, Lda, Braga, Portugal (grant number PD/BDE/127839/2016).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.096.

References

Abramowitz, J.S., 2018. Presidential address: are the obsessive-compulsive related disorders related to obsessive-compulsive disorder? A critical look at DSM-5's new category. Behav. Ther 49, 1–11. https://doi.org/10.1016/j.beth.2017.06.002.

Adams, Z.W., McClure, E.A., Gray, K.M., Danielson, C.K., Treiber, F.A., Ruggiero, K.J., 2017. Mobile devices for the remote acquisition of physiological and behavioral biomarkers in psychiatric clinical research. J. Psychiatr. Res. 85, 1–14. https://doi.org/10.1016/j.jpsychires.2016.10.019.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, (5th ed.). American Psychiatric Publishing, Arlington, VA.

Arns, M., Batail, J.-M., Bioulac, S., Congedo, M., Daudet, C., Drapier, D., et al., 2017. Neurofeedback: one of today's techniques in psychiatry? Encephale. 43, 135–145. https://doi.org/10.1016/j.encep.2016.11.003.

Barzegary, L., Yaghubi, H., Rostami, R., 2011. The effect of QEEG- guided neurofeedback treatment in decreasing of OCD symptoms. Procedia - Soc. Behav. Sci. 30, 2659–2662. https://doi.org/10.1016/j.sbspro.2011.10.519.

Begemann, M.J.H., Florisse, E.J.R., van Lutterveld, R., Kooyman, M., Sommer, I.E., 2016. Efficacy of EEG neurofeedback in psychiatry: a comprehensive overview and meta-analysis. Transl. Brain Rhythm. 1, 19–29. https://doi.org/10.15761/TBR.1000105.

Bhugra, D., Tasman, A., Pathare, S., Priebe, S., Smith, S., Torous, J., et al., 2017. The WPA- lancet psychiatry commission on the future of psychiatry. Lancet Psychiatry 4, 775–818. https://doi.org/10.1016/S2215-0366(17)30333-4.

Bruin, W., Denys, D., van Wingen, G., 2018. Diagnostic neuroimaging markers of obsessive-compulsive disorder: Initial evidence from structural and functional MRI studies. Prog. Neuro-Psychopharmacology Biol. Psychiatry In Press. https://doi.org/10.1016/j.pnpbp.2018.08.005.

Buyukturkoglu, K., Roettgers, H., Sommer, J., Rana, M., Dietzsch, L., Arikan, E.B., et al., 2015. Self-regulation of anterior insula with real-time fMRI and its behavioral effects in obsessive-compulsive disorder: a feasibility study. PLoS One 10, e0135872. https://doi.org/10.1371/journal.pone.0135872.

Carpenter, J.K., Andrews, L.A., Witcraft, S.M., Powers, M.B., Smits, J.A.J., Hofmann, S.G., 2018. Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of randomized placebo-controlled trials. Depress. Anxiety 1–13. https://doi.org/10.1002/da.22728.

Deng, X., Wang, G., Zhou, L., Zhang, X., Yang, M., Han, G., et al., 2014. Randomized controlled trial of adjunctive EEG-biofeedback treatment of obsessive-compulsive disorder. Shanghai Arch. psychiatry 26, 272–279. https://doi.org/10.11919/j.issn.1002-0829.214067.

Enriquez-Geppert, S., Huster, R.J., Herrmann, C.S., 2017. EEG-Neurofeedback as a tool to modulate cognition and behavior: a review tutorial. Front. Hum. Neurosci. 11, 1–19. https://doi.org/10.3389/fnhum.2017.00051.

Geddes, J.R., Cipriani, A., 2015. Time to abandon placebo control in pivotal phase III trials? World Psychiatry 14, 306–307. https://doi.org/10.1002/wps.20246.

Goldberg, X., Soriano-Mas, C., Alonso, P., Segalàs, C., Real, E., López-Solà, C., et al., 2015. Predictive value of familiality, stressful life events and gender on the course of obsessive-compulsive disorder. J. Affect. Disord. 185, 129–134. https://doi.org/10.1016/j.jad.2015.06.047.

Gonçalves, Ó., Camargo Batistuzzo, M., Sato, J., 2017. Real-time functional magnetic resonance imaging in obsessive-compulsive disorder. Neuropsychiatr. Dis. Treat. 13, 1825–1834. https://doi.org/10.2147/NDT.S121139.

Hammond, D.C., 2011. Placebos and neurofeedback: a case for facilitating and maximizing Placebo response in neurofeedback treatments. J. Neurother. 15, 94–114. https://doi.org/10.1080/10874208.2011.570694.

Hammond, D.C., 2004. Treatment of the obsessional subtype of obsessive compulsive disorder with neurofeedback. Biofeedback 32, 9–12.

Hammond, D.C., 2003. QEEG-guided neurofeedback in the treatment of obsessive compulsive disorder. J. Neurother. 7, 25–52. https://doi.org/10.1300/J184v07n02_03.

Hardy, R.J., Thompson, S.G., 1998. Detecting and describing heterogeneity in meta-analysis. Stat. Med. 17, 841–856 https://doi.org/10.1002/(SICI)1097-0258(19980430)17:8<841::AID-SIM781>3.0.CO;2-D.

Higgins, J.P.T., Green, S. (Eds.), 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. . Available from http://handbook.cochrane.org.

Higgins, J.P.T., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560. https://doi.org/10.1136/bmj.327.7414.557.

Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539–1558. https://doi.org/10.1002/sim.1186.

Hozo, S.P., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5, 13. https://doi.org/10.1186/1471-2288-5-13.

Koprivová, J., Congedo, M., Raszka, M., Prasko, J., Brunovský, M., Horácek, J., 2013. Prediction of treatment response and the effect of independent component neurofeedback in obsessive-compulsive disorder: a randomized, sham-controlled, double-blind study. Neuropsychobiology 67, 210–223. https://doi.org/10.1159/000347087.

LeVine, W.R., 1983. Behavioral and biofeedback therapy for a functionally impaired musician: a case report. Biofeedback Self. Regul. 8, 101–107.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of

studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6, e1000100. https://doi.org/10.1371/journal.pmed.1000100.
Loo Gee, B., Griffiths, K.M., Gulliver, A., 2016. Effectiveness of mobile technologies delivering ecological momentary interventions for stress and anxiety: a systematic review. J. Am. Med. Informatics Assoc. 23, 221–229. https://doi.org/10.1093/jamia/ocv043.
McGrath, R.E., Meyer, G.J., 2006. When effect sizes disagree: the case of r and d. Psychol. Methods 11, 386–401. https://doi.org/10.1037/1082-989X.11.4.386.
Micoulaud-Franchi, J.-A., McGonigal, A., Lopez, R., Daudet, C., Kotwas, I., Bartolomei, F., 2015. Electroencephalographic neurofeedback: level of evidence in mental and brain disorders and suggestions for good clinical practice. Neurophysiol. Clin. Neurophysiol. 45, 423–433. https://doi.org/10.1016/j.neucli.2015.10.077.
Mills, G.K., Solyom, L., 1974. Biofeedback of EEG alpha in the treatment of obsessive ruminations: an exploration. J. Behav. Ther. Exp. Psychiatry 5, 37–41. https://doi.org/10.1016/0005-7916(74)90011-1.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6, e1000097. https://doi.org/10.1371/journal.pmed.1000097.
Moreira, P.S., Marques, P., Soriano-Mas, C., Magalhães, R., Sousa, N., Soares, J.M., et al., 2017. . The neural correlates of obsessive-compulsive disorder: a multimodal perspective. Transl. Psychiatry 7, e1224. https://doi.org/10.1038/tp.2017.189.
Morris, S.B., 2008. Estimating effect sizes from pretest-posttest-control group designs. Organ. Res. Methods 11, 364–386. https://doi.org/10.1177/1094428106291059.
Morris, S.B., DeShon, R.P., 2002. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol. Methods 7, 105–125. https://doi.org/10.1037//1082-989X.7.1.105.
Nakagawa, S., Cuthill, I.C., 2007. Effect size, confidence interval and statistical significance: a practical guide for biologists. Biol. Rev. 82, 591–605. https://doi.org/10.1111/j.1469-185X.2007.00027.x.
Pearcy, C.P., Anderson, R.A., Egan, S.J., Rees, C.S., 2016. A systematic review and meta-analysis of self-help therapeutic interventions for obsessive–compulsive disorder: Is therapeutic contact key to overall improvement? J. Behav. Ther. Exp. Psychiatry 51, 74–83. https://doi.org/10.1016/j.jbtep.2015.12.007.
Pigott, H.E., Cannon, R., Trullinger, M., 2018. The fallacy of Sham-controlled neurofeedback trials: a reply to Thibault and Colleagues (2018). J. Atten. Disord 108705471879080. https://doi.org/10.1177/1087054718790802.
Rance, M., Walsh, C., Sukhodolsky, D.G., Pittman, B., Qiu, M., Kichuk, S.A., et al., 2018. . Time course of clinical change following neurofeedback. Neuroimage 181, 807–813. https://doi.org/10.1016/j.neuroimage.2018.05.001.
Rapp, A.M., Bergman, R.L., Piacentini, J., Mcguire, J.F., 2016. Evidence-based assessment of obsessive–compulsive disorder. J. Cent. Nerv. Syst. Dis. 8 JCNSD.S38359. https://doi.org/10.4137/JCNSD.S38359.
Rogala, J., Jurewicz, K., Paluch, K., Kublik, E., Cetnarski, R., Wróbel, A., 2016. The do's and don'ts of neurofeedback training: a review of the controlled studies using healthy adults. Front. Hum. Neurosci. 10, 1–12. https://doi.org/10.3389/fnhum.2016.00301.
Sachs, G., Erfurth, A., 2018. Obsessive compulsive and related disorders: from the biological basis to a rational pharmacological treatment. Int. J. Neuropsychopharmacol. 21, 59–62. https://doi.org/10.1093/ijnp/pyx101.
Scheinost, D., Stoica, T., Wasylink, S., Gruner, P., Saksa, J., Pittenger, C., et al., 2014. Resting state functional connectivity predicts neurofeedback response. Front. Behav. Neurosci 8, 338. https://doi.org/10.3389/fnbeh.2014.00338.
Schoenberg, P.L.A., David, A.S., 2014. Biofeedback for psychiatric disorders: a systematic review. Appl. Psychophysiol. Biofeedback 39, 109–135. https://doi.org/10.1007/s10484-014-9246-9.
Seibell, P., Hollander, E., 2014. Management of obsessive-compulsive disorder. F1000Prime Rep. 6, 1–6. https://doi.org/10.12703/P6-68.
Simon, D., Kaufmann, C., Kniesche, R., Kischkel, E., Kathmann, N., 2013. Autonomic responses and neural-cardiac coupling during individually tailored symptom provocation in obsessive-compulsive disorder. J. Anxiety Disord. 27, 635–644. https://doi.org/10.1016/j.janxdis.2013.08.005.
Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., et al., 2016. Closed-loop brain training: the science of neurofeedback. Nat. Rev. Neurosci. 18, 86–100. https://doi.org/10.1038/nrn.2016.164.
Sterne, J.A.C., Sutton, A.J., Ioannidis, J.P.A., Terrin, N., Jones, D.R., Lau, J., et al., 2011. . Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343 d4002–d4002. https://doi.org/10.1136/bmj.d4002.
Sugarman, M.A., Kirsch, I., Huppert, J.D., 2017. Obsessive-compulsive disorder has a reduced placebo (and antidepressant) response compared to other anxiety disorders: a meta-analysis. J. Affect. Disord. 218, 217–226. https://doi.org/10.1016/j.jad.2017.04.068.
Sürmeli, T., Ertem, A., 2011. Obsessive compulsive disorder and the efficacy of qEEG-guided neurofeedback treatment: a case series. Clin. EEG Neurosci. 42, 195–201. https://doi.org/10.1177/155005941104200310.
Thibault, R.T., MacPherson, A., Lifshitz, M., Roth, R.R., Raz, A., 2018. Neurofeedback with fMRI: a critical systematic review. Neuroimage 172, 786–807. https://doi.org/10.1016/j.neuroimage.2017.12.071.
Thompson, S.G., Higgins, J.P.T., 2002. How should meta-regression analyses be undertaken and interpreted? Stat. Med. 21, 1559–1573. https://doi.org/10.1002/sim.1187.
Thorsen, A.L., Kvale, G., Hansen, B., van den Heuvel, O.A., 2018. Symptom dimensions in obsessive-compulsive disorder as predictors of neurobiology and treatment response. Curr. Treat. Options Psychiatry. https://doi.org/10.1007/s40501-018-0142-4.
Tomczak, M., Tomczak, E., 2014. The need to report effect size estimates revisited. An overview of some recommended measures of effect size. Trends Sport Sci. 1, 19–25.
Van Ameringen, M., Turna, J., Khalesi, Z., Pullia, K., Patterson, B., 2017. There is an app for that! The current state of mobile applications (apps) for DSM-5 obsessive-compulsive disorder, posttraumatic stress disorder, anxiety and mood disorders. Depress. Anxiety 34, 526–539. https://doi.org/10.1002/da.22657.
Versluis, A., Verkuil, B., Spinhoven, P., van der Ploeg, M.M., Brosschot, J.F., 2016. Changing mental health and positive psychological well-being using ecological momentary interventions: a systematic review and meta-analysis. J. Med. Internet Res. 18, e152. https://doi.org/10.2196/jmir.5642.

1. Supplementary material

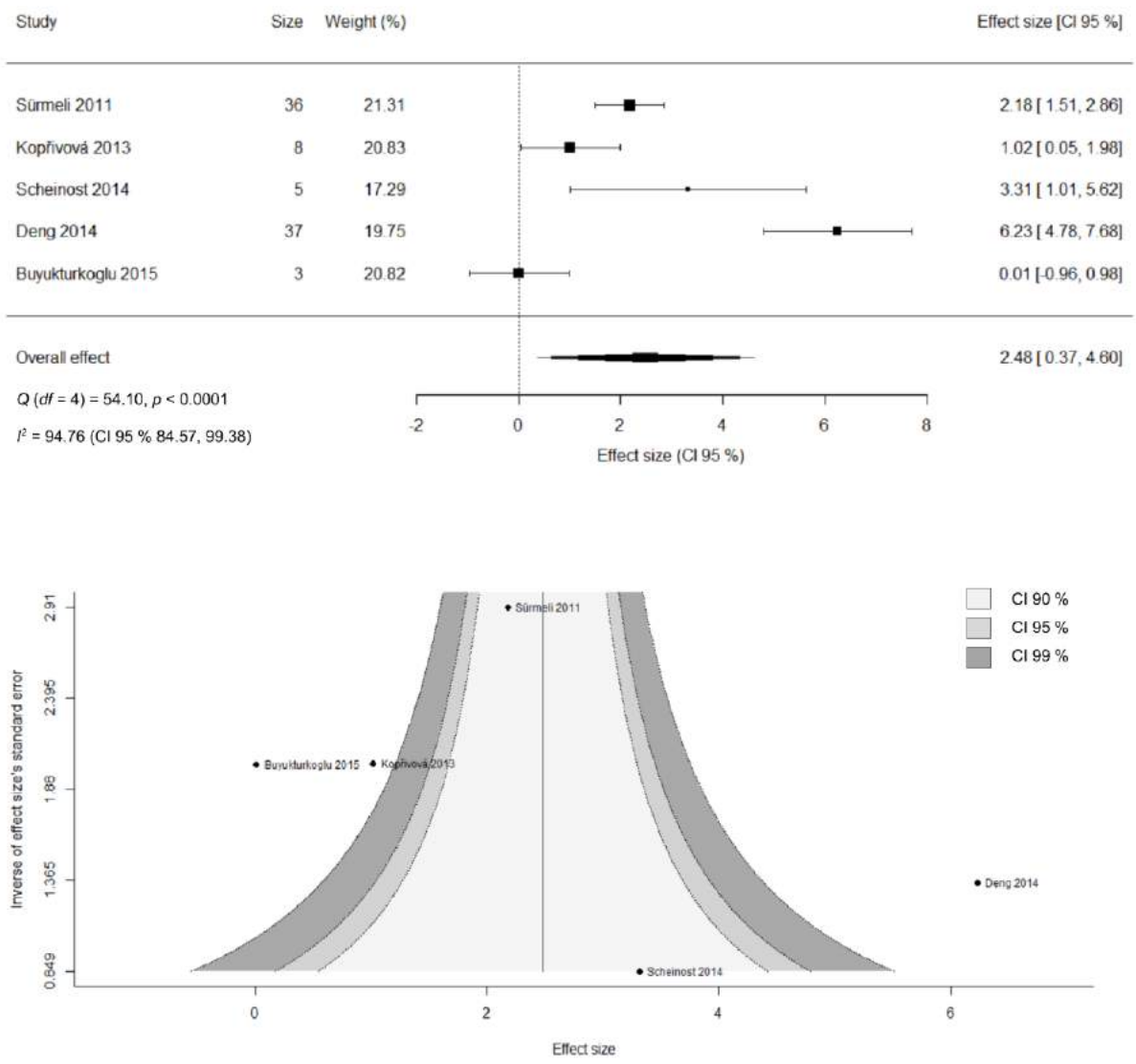


Figure S1 Forest (top) and funnel (down) plot representing the meta-analysis results for a correlation coefficient of 0.1. Studies' citation lack "*et al.*" for better visualization purpose. CI = Confidence interval; *Q* = Heterogeneity; I^2 = Inconsistency.

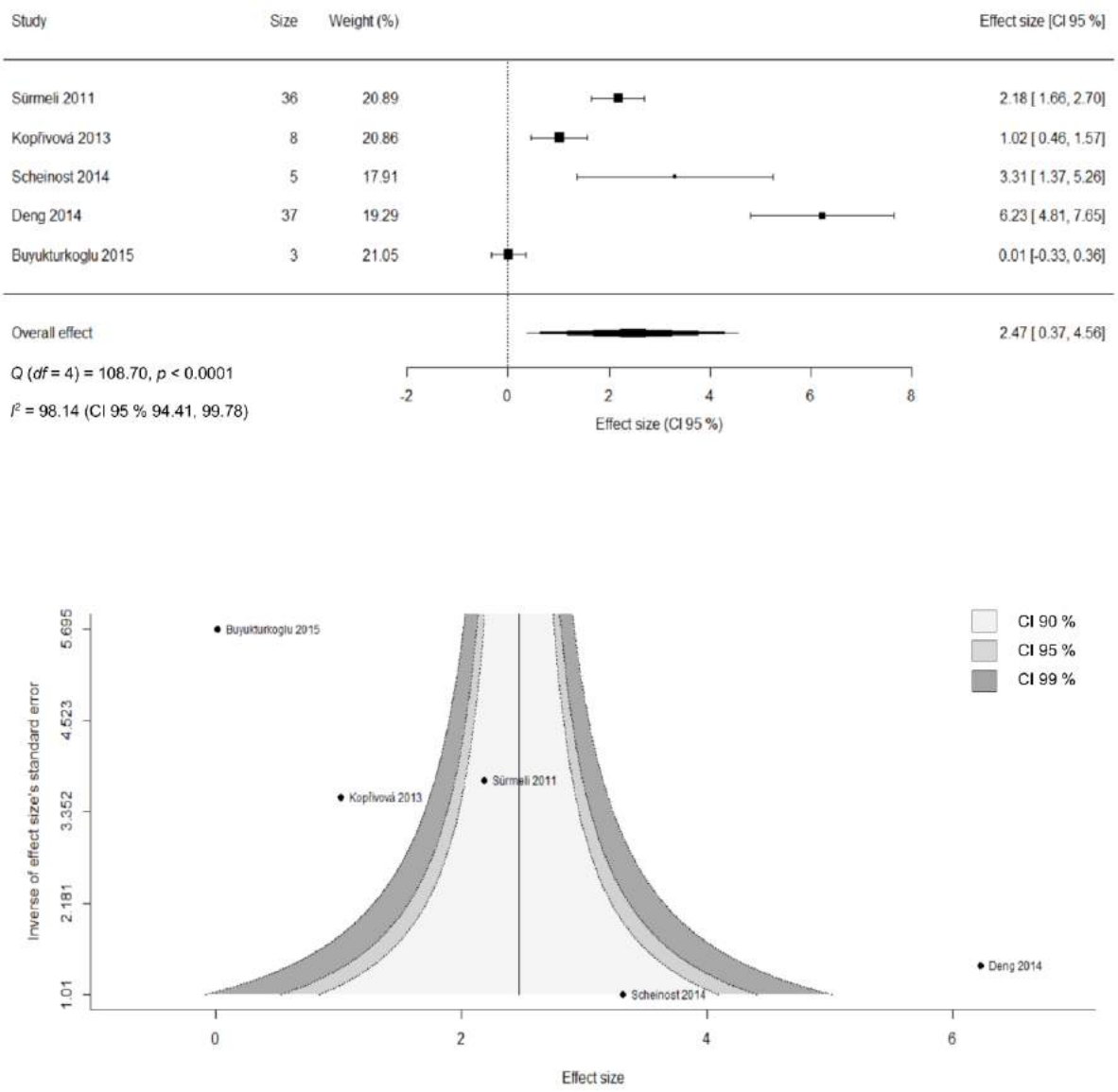


Figure S2 Forest (top) and funnel (down) plot representing the meta-analysis results for a correlation coefficient of 0.9. Studies' citation lack "*et al.*" for better visualization purpose. CI = Confidence interval; *Q* = Heterogeneity; I^2 = Inconsistency.

CHAPTER VI

Functional magnetic resonance imaging neurofeedback leads to a long-term symptomatic reduction in treatment-resistant patients with obsessive-compulsive disorder

Sónia Ferreira, Maria Picó-Pérez, Mafalda Sousa, Rita Vieira, Ricardo Magalhães, Ana Coelho, José Miguel Pêgo, Pedro Morgado

Ongoing work

Functional magnetic resonance imaging neurofeedback leads to a long-term symptomatic reduction in treatment-resistant patients with obsessive-compulsive disorder

Sónia Ferreira[1,2,3], Maria Picó-Pérez[1,2,3], Mafalda Sousa[1,2,3], Rita Vieira[1,2,3], Ricardo Magalhães[1,2,3], Ana Coelho[1,2,3], José Miguel Pêgo[1,2,3], Pedro Morgado[1,2,3]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [2]ICVS-3Bs PT Government Associate Laboratory, Braga/Guimarães, Portugal; [3]Clinical Academic Center-Braga (2CA), Braga, Portugal

1. Abstract

Obsessive-compulsive disorder (OCD) is a severe condition with a profound impact on the health, social, and professional functioning of the patients. More than one-third of the patients do not achieve remission of the symptoms after first-line treatment with cognitive-behavioral therapy and selective serotonin reuptake inhibitor medication. Neurofeedback is a promising technique that allows the non-invasive self-regulation of neural activity associated with symptomatic manifestation. Previous literature reported preliminary evidence of positive effects of functional magnetic resonance imaging (fMRI) neurofeedback on OCD symptoms. However, these studies have small samples and/or were not controlled. Additionally, these studies did not involve treatment-resistant patients. We implemented a sham-controlled, double-blinded fMRI neurofeedback protocol to target hyperactivity in orbitofrontal regions in treatment-resistant OCD patients with contamination/cleaning symptoms. The protocol had two sessions of neurofeedback (72 min of total training). The patients included were under treatment-as-usual. Our preliminary results with the experimental group (n = 10 patients) demonstrated decreased OCD and stress symptoms three months after the neurofeedback sessions. Moreover, immediately after the neurofeedback sessions, we observed increased negative functional connectivity between orbitofrontal and temporoparietal areas, and increased brain activity in a dorsolateral prefrontal/premotor region during symptomatic provocation. These brain functional changes might be associated with better control over obsessions. Our results need further validation with the sham-control group but highlight the efficacy of fMRI neurofeedback for refractory OCD and the necessity of prolonged neurofeedback protocols.

2. Introduction

Obsessive-compulsive disorder (OCD) is a severe chronic illness with a lifetime prevalence of 1 to 3 % (Hirschtritt et al., 2017; Stein et al., 2019). It is characterized by recurrent intrusive thoughts (obsessions) and repetitive or ritualistic actions or mental acts intended to diminish the anxiety and distress elicited by obsessions (compulsions) (American Psychiatric Association, 2013). OCD symptomology is very heterogeneous with distinct dimensions for obsessions and compulsions, for example, contamination obsessions associated with cleaning compulsions, or harm obsessions associated with checking compulsions (American Psychiatric Association, 2013). OCD is characterized by structural and functional alterations in the orbitofrontal (OFC), ventromedial prefrontal and anterior cingulate cortices, and thalamic and striatal regions - cortico-striato-thalamo-cortical pathway (Bruin et al., 2019; Moreira et al., 2017). These regions and other areas outside these circuits (amygdala, anterior insula, and temporal and occipital gyri) are hyperactivated during emotional processing in OCD including symptom-provoking paradigms (Frydman et al., 2016; Maria Picó-Pérez et al., 2020; A. L. Thorsen et al., 2018). Recent studies also reported hypoconnectivity within the salience, frontoparietal, and default-mode brain networks in OCD (Gürsel et al., 2018), and enhanced functional connectivity (FC) between orbitofrontal and striatal regions, and between frontal and amygdalar areas (MacNamara et al., 2016).

First-line treatment guidelines for OCD include cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medication. However, only one-third of the patients are treated with CBT (Brakoulias et al., 2019) and at least 40 % of the patients remain untreated or do not seek help (Burchi et al., 2018). Moreover, at least 30 % of the patients do not achieve sustained remission after treatment (Burchi et al., 2018; Gershkovich et al., 2017; Zhou et al., 2019). Invasive techniques such as neurosurgery, deep brain stimulation, and ablative surgery might be used for treatment-refractory cases.

Nowadays, non-invasive neuromodulation methods such as transcranial magnetic stimulation and transcranial direct current stimulation may be an alternative choice for OCD patients resistant to first-line treatments (Gershkovich et al., 2017; Hirschtritt et al., 2017; Rachid, 2019; Trevizol et al., 2016). Neurofeedback is a non-invasive intervention that allows real-time self-modulation of dysfunctional brain regions. Neurofeedback is mostly implemented with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) (Gonçalves et al., 2016; J.H. Begemann et al., 2016; Micoulaud-Franchi et al., 2015; Schoenberg & David, 2014; Sitaram et al., 2016). fMRI has a better spatial resolution to localize brain regions, especially for activity in deep/subcortical areas (Lubianiker et al., 2019; Meir-Hasson et al., 2014; D Scheinost et al., 2013; Sitaram et al., 2016; Sürmeli & Ertem, 2011; Zotev et al., 2014).

Neurofeedback is commonly applied to an experimental group and a control group to account for placebo effects since the participants are always aware of this treatment approach. Yoked/sham feedback with information from the brain activity of another participant or another brain region is often used as a control condition (Linhartová et al., 2019).

Previous authors using fMRI (Buyukturkoglu et al., 2015; Rance et al., 2018; Dustin Scheinost et al., 2014) and EEG (Barzegary et al., 2011; Deng et al., 2014; D. Corydon Hammond, 2003; D C Hammond, 2004; Koprivová et al., 2013; Sürmeli & Ertem, 2011) neurofeedback reported reduction of OCD symptoms after the intervention (S. Ferreira, Pêgo, et al., 2019). The fMRI studies pointed to an improvement of OCD symptomatology but lacked validation with large samples and/or were not controlled. Moreover, these studies did not specifically involve treatment-resistant OCD patients. The first non-controlled study with five contamination patients reported an improvement of OCD symptoms after the regulation of orbitofrontal responses (Dustin Scheinost et al., 2014). Another study examined three contamination patients regulating their insular activity while providing monetary feedback (Buyukturkoglu et al., 2015). The authors reported decreased activation in the target region. The most recent study pooled together checking and contamination OCD patients (ten patients for the experimental and seven for the sham group) and Tourette syndrome patients using the same neurofeedback protocol as Scheinost et al. (2014). They reported symptomatic improvement after three months of the last neurofeedback session (Rance et al., 2018). However, the authors did not report the outcomes separately for the OCD group. Thus, our study intends to explore the efficacy of fMRI neurofeedback for treatment-resistant OCD patients using a controlled, double-blinded design. Based on previous results, we hypothesize that OCD-related symptoms (mainly obsessions, compulsions, and anxiety) and brain activity in the target region will decreased after neurofeedback. Moreover, we expect increased FC in the DMN, FPN and salience networks after neurofeedback, and reduced FC between the frontal cortex and the amygdala/striatum.

3. Methods

The experimental protocol was pre-registered on ClinicalTrials.gov (NCT03956771). The protocol description follows the CRED-nf checklist (Tomas Ros, Stefanie Enriquez-Geppert, Vadim Zotev, Kymberly Young, Guilherme Wood et al., 2019).

a. Participants

OCD individuals with age between 18 and 65 years were recruited at the Psychiatry Unit of *Hospital de Braga* (non-randomized convenience sample). The OCD diagnosis was established by a psychiatrist (PM) based on the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders. Patients were diagnosed with treatment resistance if at least three SSRIs trials were applied without response or with a minimal response for at least 12 weeks at the maximum dose (Gershkovich et al., 2017; Seibell & Hollander, 2014). Only patients with primary contamination-related obsessions were included because the neurofeedback stimulus was developed with contamination pictures (detailed information in the next sections). Patients were receiving treatment as usual (medication and/or CBT). Exclusion criteria were concomitant psychiatric or neurological illness, diabetes (D'Esposito et al., 2003), substance abuse/dependence in the past 6 months (except nicotine/caffeine), acute suicidal ideation, or magnetic resonance imaging (MRI) contraindications (e. g. pregnancy, major head trauma, severe claustrophobia, severe back pain, or body ferromagnetic materials/prosthesis/implants).

All participants signed an informed consent. The study was approved by the ethics committees of *Hospital de Braga* (*Comissão de Ética para a Saúde*) and University of Minho (*Subcomissão de Ética para as Ciências da Vida e da Saúde*) and respected the Declaration of Helsinki principles.

b. Experimental protocol design

Our protocol consisted of five distinct visits in time. Visits 1 to 4 occurred over a period of two weeks. Visit 5 took place approximately three months after visit 4 (**Figure 1**) (Micoulaud-Franchi et al., 2015; Rance et al., 2018; Randell et al., 2018). Visit 1 was a baseline assessment before starting the neurofeedback training and was repeated on visit 4 to evaluate the neurofeedback impact. First, patients underwent a magnetic resonance imaging (MRI) session with anatomical and resting-state acquisitions and the OFC localizer stimulus. Then, a psychometric evaluation was performed by trained psychologists (MS and RV) followed by the strategies developing session. On visit 2 and 3, patients underwent the neurofeedback training inside the scanner. Three runs of neurofeedback (36 min in total) were used per day (Buyukturkoglu et al., 2015; Radua et al., 2018; Rance et al., 2018; Randell et al., 2018; Dustin Scheinost et al., 2014; Schoenberg & David, 2014). During visit 5, we repeated the psychometric

evaluation from visit 1 to examine the long-term effects of neurofeedback training (Rance et al., 2018). The experimental protocol is further explained in the next sections.

c. Psychometric evaluation

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to evaluate the severity of OCD (visit 1, 4, and 5) (Castro-Rodrigues et al., 2018; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989). We assumed response to the neurofeedback intervention of at least a 35 % reduction in Y-BOCS score three months after the protocol (visit 5). A partial response was defined as a reduction in the Y-BOCS score between 25 and 34 % (Burchi et al., 2018; Fornaro, 2019; Gershkovich et al., 2017; Mataix-Cols et al., 2016). The Obsessive-Compulsive Inventory-Revised (OCI-R) was also used to quantify OCD severity and symptomatic dimensions (visit 1 and 5; this scale reports to the previous month) (Abramowitz & Deacon, 2006; Foa et al., 2002). We applied the Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale (HDRS) to measure the severity of anxiety and depression symptoms, respectively (visit 1, 4, and 5) (Hamilton, 1959, 1960). State and trait anxiety were also assessed with the State-Trait Anxiety Inventory (STAI) (visits 1, 4, and 5) (Silva & Campos, 1998; Spielberger et al., 1999). The 10-items Perceived Stress Scale (PSS-10) was also applied on visits 1 and 5 to measured self-perceived stress levels (this scale reports to the previous month) (S. Cohen et al., 1983; P. Morgado et al., 2013; Trigo et al., 2010). We also applied the Emotion Regulation Questionnaire (ERQ) to measure the habitual use of reappraisal and suppression emotion regulation strategies (visit 1, 4 and 5) (Gross & John, 2003; Vaz et al., 2014). **Figure 1** represents the timeline for the psychometric evaluation. The psychologists performing the evaluation were initially blinded to the participants' group assignment. However, unblinding may have occurred after discussion of the results within the team.

Psychometric data were analyzed with JASP (version 0.11.1; JASP Team, University of Amsterdam, The Netherlands) using non-parametric tests given the reduced sample size: Friedman test (χ^2) for repeated measures in time (visit 1, 4, and 5; post-hoc Wilcoxon signed-rank one-sided tests [*W*] with Bonferroni correction for multiple comparisons for statistically significant changes [p_{bonf}]); the OCI-R and PSS-10 score changes were evaluated with the Wilcoxon signed-rank one-sided test (visit 1 and 5). Bonferroni correction was applied for subscales analysis. Differences were considered statistically significant if *p*-value was lower than 0.05.

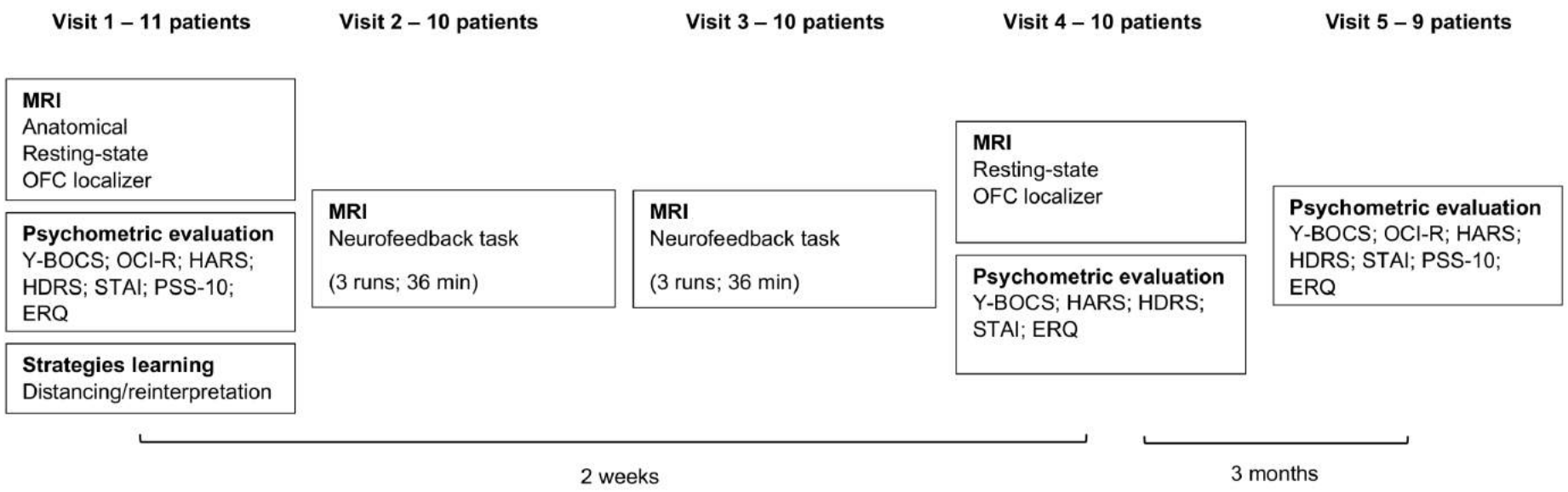


Figure 1 Representation of the experimental protocol timeline. MRI – magnetic resonance imaging; OFC – orbitofrontal cortex; Y-BOCS - Yale–Brown Obsessive Compulsive Scale; OCI-R - Obsessive Compulsive Inventory Revised; HARS – Hamilton Anxiety Rating Scale; HDRS – Hamilton Depression Rating Scale; STAI - State-Trait Anxiety Inventory; PSS-10 – Perceived Stress Scale; ERQ – Emotional Regulation Questionnaire.

d. Strategies developing session

Emotional regulation is often performed with cognitive reappraisal strategies. These strategies involve reflecting on a situation in a different way to alter its emotional impact. Reappraisal may be achieved with reinterpretation or distancing tactics. During distancing, there is a simulation of the situation adopting the perspective of an uninvolved observer. For reinterpretation, the participant changes the situation outcome or meaning to achieve a more positive valuation (Maria Picó-Pérez et al., 2017; Powers & LaBar, 2019)**.** During visit 1, a psychologist taught the patients how to use distancing and reinterpretation strategies while exemplifying with contamination-related pictures. They advised the participants to use these tactics during the neurofeedback sessions (Hampson et al., 2012). The participants were reminded of the reappraisal tactics on the neurofeedback days.

e. MRI acquisition

i. Stimuli

To create the fMRI stimuli (OFC localizer and neurofeedback task), we combined three datasets of contamination-related pictures previously validated with OCD patients: the Maudsley Obsessive–Compulsive Stimuli Set (Mataix-Cols et al., 2009), the Berlin Obsessive Compulsive Disorder-Picture Set (Simon et al., 2012), and the Yale School of Medicine set (Hampson et al., 2012). We obtained a total of 353 pictures from which we randomly selected 336 pictures for stimuli. The remaining pictures were used to train the participants before engaging in fMRI tasks. Each picture was only used once to avoid habituation effects, except for the localizer stimulus because we wanted to evaluate changes in picture ratings.

1. Localizer stimulus

Forty-eight contamination-related and 48 neutral pictures were used on visit 1 to localize the OFC region to modulate during the neurofeedback sessions (Buyukturkoglu et al., 2015; Hampson et al., 2012; Rance et al., 2018; Dustin Scheinost et al., 2014). The neutral pictures were selected from the International Affective Picture System (Lang et al., 1997, 2005) and were the same used on the Maudsley Obsessive–Compulsive Stimuli Set (Mataix-Cols et al., 2009). Before the contamination pictures, we

presented the text cue “Imagine” (4 s) and instructed the patients to experience the situation described by the image, allowing themselves to feel the emotions provoked. For the neutral pictures, the text cue was “Observe” (4 s) and the instruction consisted of visualizing the pictures. Following the cue, 4 pictures were shown (5 s each). After each picture set, we asked the participants to rate the images (4 s) in accordance to the level of emotional negativity felt (1 – neutral to 4 – extremely negative). We chose the 4-items Likert scale to match the number of buttons available in the response pads. Twelve blocks of contamination and 12 blocks of neutral pictures were used in random order (equal among patients and on visit 1 and 4) with a 12 s baseline between blocks (grey screen) [supplementary **Figure S1**]. The localizer stimulus was repeated on visit 4 to evaluated brain activity differences and changes in picture ratings induced by the neurofeedback training. The stimulus was developed with PsyhcoPy3 (version v1.90.1, University of Nottingham)(Peirce, 2007, 2008).

2. Neurofeedback stimulus

The neurofeedback task was created based on an adaptation of the OpenNFT software (Koush, Ashburner, Prilepin, Sladky, Zeidman, Bibikov, Scharnowski, Nikonorov, & De Ville, 2017; Koush, Ashburner, Prilepin, Sladky, Zeidman, Bibikov, Scharnowski, Nikonorov, & Van De Ville, 2017). This software incorporates Python (Python Software Foundation) and MATLAB (The MathWorks Inc, USA) to acquire and process MRI data in real-time, and to display visual stimulus with feedback information. We randomly selected 48 contamination pictures per run. The pictures and their order were the same for all participants for each run. After the text cue “Imagine” (5 s), we instructed the patients to experience the situation described by the image, allowing themselves to feel the emotions provoked. For the text cue “Regulate” (5 s), the instruction consisted of regulating the activity of OFC based on the feedback provided by using the reappraisal strategies learned on visit 1 (Linhartová et al., 2019). In this way, we induced the symptoms during the imagine blocks to increase the OFC activity and then asked the patients to reduce this activity during the regulate blocks (Maria Picó-Pérez et al., 2017). We adopted this method to approach real-life symptomatic manifestation (Lubianiker et al., 2019). Following the cue, 4 pictures were shown (10 s each) (Radua et al., 2018; Thibault et al., 2018). Six blocks of imagine and 6 blocks of regulate were used in alternating order with a 15 s baseline between blocks (gray screen) [12 min per run; **Figure 2**]. Three runs of neurofeedback were performed on each day (a total of 6 runs for the all protocol; 72 min of training) (Buyukturkoglu et al., 2015; Radua et al., 2018; Rance et al., 2018; Randell et al., 2018; Dustin Scheinost et al., 2014; Thibault et al., 2018).

The feedback was continuously provided during the regulate blocks for each data volume (every 1 s). The feedback was estimated based on the blood-oxygen-level-dependent signal change in the OFC region compared to the median value during previous imagine blocks. The feedback values were displayed as the transparency of the pictures (Aranyi, Cavazza, et al., 2015; Aranyi, Charles, et al., 2015; Jiang et al., 2017; Sokunbi et al., 2014). If the patients were able to decrease the OFC activity, the picture became more transparent. Otherwise, the picture became sharper (**Figure 2**). Previous studies used more complex stimuli with simultaneous display of pictures, the feedback instruction, and sometimes the brain activity graph (Buyukturkoglu et al., 2015; Hampson et al., 2012; Rance et al., 2018; D Scheinost et al., 2013; Dustin Scheinost et al., 2014). Despite this, previous authors suggest that proportionate, simple, and immediate visual feedback is better (Arns et al., 2017; Mel'nikov et al., 2018; Micoulaud-Franchi et al., 2015). For this reason, we followed this approach to avoid decreases in attention to the pictures and to reduce the cognitive load. We chose a unidirectional regulation of the OFC because OCD symptomatology is associated with hyperactivation of this region (A. L. Thorsen et al., 2018). Thus, we would expect symptomatic worsening after the upregulation of the OFC during neurofeedback (Linhartová et al., 2019; Sorger et al., 2019). We analyzed changes in the average OFC feedback signal across the six regulation runs with the Friedman test. Post-hoc paired one-sided Wilcoxon tests were also performed with Bonferroni correction to measure differences between the first and last run of neurofeedback.

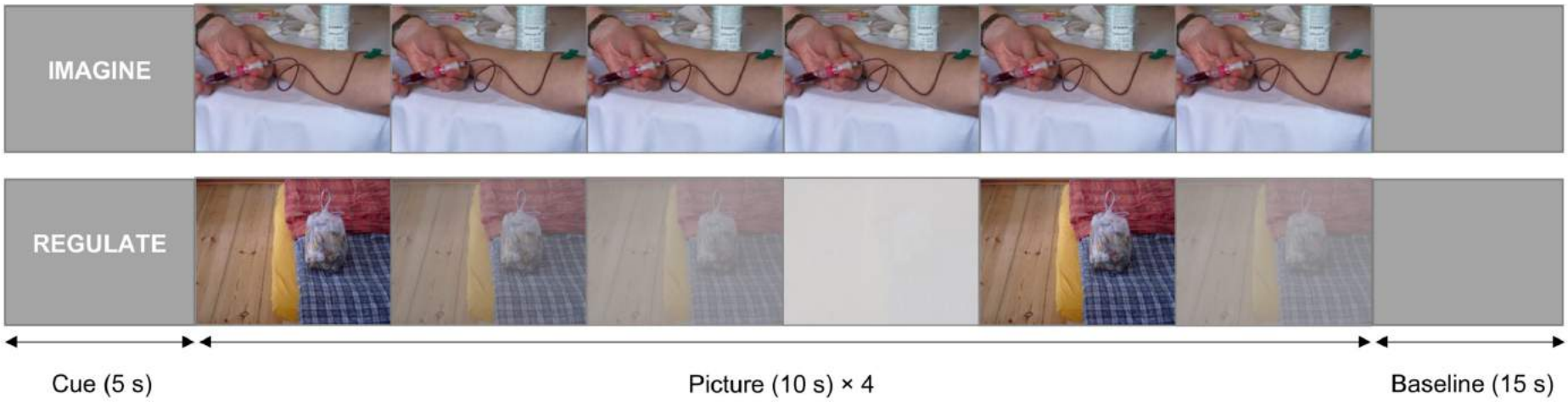


Figure 2 Representation of the neurofeedback stimulus. Six imagine and 6 regulate blocks were alternately presented with 15 s baseline intervals. Each block had 4 contamination pictures. The feedback was presented as the contamination picture transparency. More transparency corresponded to lower orbitofrontal cortical activity during the regulate blocks. The displayed pictures belong to the Berlin Obsessive Compulsive Disorder-Picture Set (Simon et al., 2012).

The neurofeedback stimulus was explained to the participants before the MRI session with training pictures. We instructed them to use the reappraisal strategies to make the pictures disappear by reducing the brain response in a region associated with the disorder. We also pointed out that the regulation was not working when the pictures became clearer, and that changing the regulation strategy could help. Moreover, we informed that the feedback could be slightly delayed due to the hemodynamic response effect, and that it could take more time for some individuals to achieve the desired regulation state (Mel'nikov et al., 2018; Stoeckel et al., 2014).

We evaluated the participants' motivation, treatment expectations, effort exerted, and sense of success with a questionnaire after the neurofeedback sessions. This questionnaire also checked if the participant believed that the neurofeedback matched his/her effort to regulate brain activity, the regulation strategies used, and beneficial/adverse effects of neurofeedback (Garrison et al., 2013; Sorger et al., 2019; Thibault et al., 2018; Tomas Ros, Stefanie Enriquez-Geppert, Vadim Zotev, Kymberly Young, Guilherme Wood et al., 2019).

ii. MRI sequences

The participants were scanned on a 3 T scanner (MAGNETOM Verio, Siemens Medical Solutions, Germany) using a 12-channel head coil. The stimuli were back-projected on a screen and the participants' responses were collected with the Lumina 3G Controller and the LS-PAIR response pads (Cedrus Corporation, USA).

For functional images, a multi-band echo-planar imaging sequence was acquired (CMRR EPI 2D [R2016A, Center for Magnetic Resonance Research, University of Minnesota, USA](Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013)): bandwidth 1546 Hz/Px, multi-band acceleration factor 4, 44 interleaved slices, repetition time (TR) 1000 ms, echo time (TE) 27 ms, field of view (FOV) 200 × 200 mm^2, flip angle (FA) 62°, iso planar resolution 3 mm^3, 66 × 66 matrix size, and slice thickness 3 mm. To optimize the sensitivity in OFC, we used a tilted acquisition of 30° relative to the anterior-posterior commissure line. In total, 965 volumes (≃ 16 min) were acquired for the localizer task, 735 volumes (≃ 12 min) for each neurofeedback run, and 430 volumes (≃ 7 min) for the resting-state images. We instructed the patients to close their eyes, relax, and to let their minds wander freely during the resting-state acquisitions. A field map gradient echo sequence was acquired to account for the magnetic field inhomogeneity (bandwidth 283 Hz/Px, 44 interleaved slices, TR 700 ms, TE 5.19 ms, FOV 200 × 200

mm^2, FA 54°, iso planar resolution 3 mm^3, 66 × 66 matrix size, and slice thickness 3 mm). One high-resolution T1 weighted magnetization-prepared rapid acquisition with gradient-echo sequence with 1 × 1 × 1 mm^3 voxel size, TR 2450 ms, TE 4.13 ms, interslice time 1100 ms, FA 9°, FOV 256 × 256 mm^2, 256 × 256 matrix size, bandwidth 130 Hz/Px, 176 ascending slices, and GRAPPA acceleration factor of 2 was also acquired (**Figure 1** represents the timeline for the MRI acquisitions).

iii. MRI analysis

1. Localizer stimulus processing to define OFC target

The localizer functional scans were processed with the Statistical Parametric Mapping (SPM) version 12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UK) using MATLAB version R2018a (The MathWorks Inc., USA) because OpenNFT uses SPM functions during real-time data processing. The preprocessing procedures included: slice-timing correction using the first slice as a reference; realignment to the mean volume of the acquisition; spatial smoothing with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel; high pass temporal filtering at 128 s (Koush, Ashburner, Prilepin, Sladky, Zeidman, Bibikov, Scharnowski, Nikonorov, & De Ville, 2017). Six predictors were used to construct the General Linear Model (GLM) representing the cue, observe, imagine, rating, and baseline blocks. The functional map of the contrast imagine > observe was defined inside of an OFC mask. The OFC mask was created with the WFU PickAtlas plugin for SPM (http://fmri.wfubmc.edu/software/pickatlas) using Automated Anatomical Labeling regions (Frontal_Sup_Orb_L and R; Frontal_Mid_Orb_L and R; Frontal_Inf_Orb_L and R). The OFC mask was transformed into the native space of each subject. Lastly, we defined the neurofeedback target region centered around the peak voxel with a radius of 10 mm (supplementary **Figure S2**).

2. MRI data preprocessing

Preprocessing was performed with the fMRIPrep software (version 1.4.1; RRID:SCR_016216 (Esteban, Markiewicz, et al., 2019)). The anatomical sequence was corrected for intensity non-uniformity (Avants et al., 2008; Tustison et al., 2010), skull-stripped, and segmented into the cerebrospinal fluid, white-matter and gray-matter (Zhang et al., 2001). The brain surfaces were reconstructed (Dale et al., 1999) and a brain mask was estimated (Klein et al., 2017). The images were non-linearly transformed

into standard space using the ICBM 152 Nonlinear Asymmetrical template (version 2009c; MNI152NLin2009cAsym (Fonov et al., 2011)).

For functional scans, a reference volume and the skull-stripped version were created using the fMRIPrep standard methodology. The deformation field to correct for susceptibility distortions was calculated based on the co-registered field map (Glasser et al., 2013). Based on the susceptibility distortion, an unwarped functional reference was calculated for co-registration with the anatomical reference (Greve & Fischl, 2009). Head-motion parameters from the functional reference (the transformation matrices and six corresponding rotation and translation parameters) were estimated before spatiotemporal filtering (Jenkinson, 2002). The functional sequences were slice-time corrected (Cox, 1996). The corrected time-series were resampled onto native space by applying a single composite transform to correct for head-motion and susceptibility distortions. Lastly, they were resampled into MNI152NLin2009cAsym space. Subjects' sequences with mean framewise displacement (FD) higher than 0.50 mm were excluded (Power et al., 2012, 2013). We used the following confounding time-series regressors: FD, DVARS (Power et al., 2014), and region-wise global signals (within the cerebrospinal fluid and white matter). Additionally, some physiological regressors were used to allow component-based noise correction (aCompCor, estimated after high-pass filtering with a discrete cosine filter with 128 s cut-off for the anatomical variant (Behzadi et al., 2007)). The mean cerebrospinal fluid and white-matter signals, first six aCompCor components, FD, and DVARS were regressed as confounds from functional data with *fslregfilt* from FSL (version 6.0; Analysis Group, FMRIB, UK (Jenkinson et al., 2012)). Ultimately, *fslmaths* (FSL) was used for spatial smoothing (with a 6 mm FWHM kernel) and temporal filtering (between 0.01 and 0.08 Hz for resting state, and higher than 0.01 Hz for the localizer stimuli) (Esteban, Ciric, et al., 2019; Power et al., 2012, 2013).

3. Localizer stimulus changes after neurofeedback

First, we evaluated if the rating scores for contamination and neutral pictures changed after neurofeedback with repeated measures ANOVA (*F* test; two within-subject factors – visit (1 and 4) and picture (neutral and contamination). Post-hoc paired *t*-tests were carried out for statistically significant results with Bonferroni correction for multiple comparisons. The rating scores were normalized between 0 and 1 before statistical analysis (by dividing by the maximum value).

The localizer stimuli sequences were analyzed with FSL after the preprocessing steps described above. FSL *feat* was used to create the individual GLM matrices for each visit with the following regressors: cue,

baseline, imagine, observe, and rating. The latter regressor was modulated by the rating score at each block. The contrasts imagine > observe and observe > imagine were computed for each participant (Woolrich et al., 2001). Lastly, the differences induced by neurofeedback on these contrasts were estimated using non-parametric permutation methods with FSL *randomise* (paired *t*-test design; contrasts before > after and after > before; 5000 permutations; $\alpha = 0.05$ [$t = 0.95$] after threshold-free cluster enhancement [TFCE] and family-wise error rate [FWE-R] correction) (Winkler et al., 2014). The statistically significant clusters were classified with the Harvard-Oxford cortical and subcortical structural atlas (Desikan et al., 2006).

4. Resting-state changes after neurofeedback

We used independent component analysis (ICA) to analyze resting-state networks changes after neurofeedback (from visit 1 to 4) with *melodic* from FSL (C.F. Beckmann & Smith, 2004). The resting-state networks were calculated based on all resting-state sequences from all subjects after preprocessing. We used a limit of 25, 35, and 45 components (Christian F. Beckmann, 2012). We selected the output with 35 components after visual inspection of their spatial distribution to exclude noisy results (Horowitz-Kraus et al., 2015) and classification with the FINDLab templates (FSL *fslcc*; University of Standford, USA (Shirer et al., 2012)). Then, dual-regression was used to estimate the individual components from the group networks (C. Beckmann et al., 2009; Nickerson et al., 2017), and the differences induced by neurofeedback were estimated using non-parametric permutation methods with *randomise* (paired *t*-test design; contrasts before > after and after > before; 5000 permutations; $\alpha = 0.05$ after TFCE and FWE-R correction) (Winkler et al., 2014).

We also assessed alterations in the functional connectome induced by neurofeedback (paired *t*-test; contrasts before > after and after > before). First, we extracted the averaged time-series inside the Shen Atlas (268 regions/nodes (X. Shen et al., 2013)) for each resting-state sequence. We estimated the Pearson's correlation between time-series and performed a Fisher's Z transformation to estimate the functional connectivity matrices. We applied Network Based Statistics (NBS) to correct for multiple comparisons among the connections in the network taking into account our statistical hypothesis (Zalesky et al., 2010). NBS starts by testing the hypothesis at every connection in the network and then determines which connections exceed the predefined test statistic threshold. We explored a range of thresholds corresponding to *p*-values between 0.01 and 0.00001. After, the software estimates topological clusters

(connected graph components) among the supra-threshold connections. Lastly, NBS calculates the FWE-R-corrected *p*-value for each component using random permutations (n = 5000, FWE-R-corrected network significance of 0.05).

Additionally, we analyzed changes after neurofeedback (from visit 1 to 4) in whole-brain FC with the target OFC region (seed-based FC). We calculated the participants' connectivity maps with FSL *feat* by estimating the correlation maps with the individual OFC regions (5 mm radius; supplementary **Figure S2**) (Woolrich et al., 2001). Then, the differences induced by neurofeedback were estimated using non-parametric permutation methods with *randomise* (paired *t*-test design; contrasts before > after and after > before; 5000 permutations; α = 0.05 after TFCE and FWE-R correction) (Winkler et al., 2014).

Statistically significant clusters were classified with the Harvard-Oxford cortical and subcortical structural atlas (Desikan et al., 2006).

4. Results

a. Participants description

The OCD patients were blinded and split into two groups: the real neurofeedback group (treatment) and the sham neurofeedback group (control) (Schoenberg & David, 2014). The treatment group received feedback information from real brain activity, while the sham group will be provided with feedback from a participant in the treatment group to account for placebo effects (Rance et al., 2018; Stoeckel et al., 2014). The treatment group was acquired first to determine the feedback values before recruiting the sham group. We included eleven patients in the treatment group. We did not achieve the predetermined sample size due to recruitment difficulties (30 patients [15 per group] based on the effect size of 0.30 [$\alpha = \beta = 0.05$, repeated measures ANOVA within-between interaction] and a 30 % dropout rate) (J.H. Begemann et al., 2016; Pearcy et al., 2016; Randell et al., 2018). We are now starting to include patients in the sham group. One patient dropped out after visit 1 due to discomfort with the contamination stimuli. Another participant dropped out after visit 4. **Table 1** summarizes the participants' sociodemographic and clinical information.

b. Psychometric analysis

Table 1 summarizes the statistically significant differences and the group median scores for the psychometric scales on visits 1, 4, and 5. **Figure 3** and **4** represents the psychometric variations across visits.

Concerning Y-BOCS, two patients responded after finishing the neurofeedback training. After three months, two patients were partial responders and one patient was a responder. The median change in the Y-BOCS total score was -12.15 (19.00) % after neurofeedback and -7.70 (26. 70) % three months after. Two of the participants who improved after three months changed their medication between visit 4 and visit 5. A patient with symptomatic worsening gave up psychotherapy in this period.

The total OCI-R score decreased three months after neurofeedback (W= 36.00; p = 0.007; rank-biserial correlation RC = 1.00). Lastly, the PSS-10 score diminished three months after neurofeedback (W = 39.00; p = 0.029; RC = 0.73).

c. Neurofeedback outcomes

We described the main parameters associated with the neurofeedback training in **Table 2**. All patients underwent two sessions of neurofeedback spaced by median (interquartile range) 5.00 (2.75) days. Most of the participants used distancing and reinterpretation strategies among others (e.g. relaxation). The patients reported feeling better self-control and were more relaxed and motivated during/after neurofeedback. They also described frustration due to the lack of regulation capacity, headache, tiredness, and feeling disgusted by the pictures during/after neurofeedback. The feedback signal (OFC activity change during regulation blocks compared to imagine blocks) did not change across the neurofeedback runs ($\chi^2(2) = 6.78$, $p = 0.238$, Kendall's W [KW] = 0.33). Moreover, the feedback signal was not different between the first (run 1) and the last neurofeedback run (run 6) (W= 26.00, p_{bonf} = 1.00, RC = 0.16). One participant was excluded from this analysis because the values from the first neurofeedback session were not saved automatically.

d. Localizer stimulus

The patients rated equally the pictures before and after neurofeedback (visit main effect $F_{(1,8)}$ = 1.91, p = 0.205, $\eta^2 = 4\times10^{-3}$), and the rating scores over time were not statistically different within the picture

category (interaction effect visit × picture $F_{(1,8)} = 0.14$, $p = 0.721$, $\eta^2 = 1\times10^{-3}$). However, the patients rated higher the contamination pictures compared to the neutral pictures in both visits (picture main effect $F_{(1,8)} = 42.54$, $p = 1.837\times10^{-4}$, $\eta^2 = 0.73$; post-hoc paired *t*-tests contamination versus neutral pictures - visit 1 $t_{(9)} = 6.07$, $p_{bonf} = 4.303\times10^{-4}$, $d = 2.02$; visit 4 $t_{(9)} = 5.75$, $p_{bonf} = 6.842\times10^{-4}$, $d = 1.92$; contamination visit 1 – mean ± standard deviation 0.63 ± 0.07, and visit 4 - 0.60 ± 0.11; neutral visit 1 - 0.29 ± 0.11, and visit 4 - 0.28 ± 0.11). One patient was excluded from this analysis because he answered once during visit 1. Despite the lack of changes in the ratings, we found a statistically significant increase in brain response after neurofeedback training for the contrasts imagine > observe in a cluster comprising mostly the right middle frontal/precentral gyrus (**Table 3** and **Figure 5**). The activation pattern before and after neurofeedback is also represented in **Figure 5**.

Table 1 Description of sociodemographic, clinical and psychometric data from the treatment group (n = 10). The statistical differences from the Friedman test among visit 1, 4 and 5 are also represented with Kendall's W (KW) effect size (Wilcoxon test between visit 1 and 5 for the OCI-R and PSS-10 scale with rank-biserial correlation effect size [RC]). Statistically significant values are marked in bold (p_{bonf} Bonferroni correction).

		Visit 1	Visit 4	Visit 5	Statistical results
Age (years)		28.50 (10.50)	-	-	-
Gender (female:male)		7:3	-	-	-
Education (years)		15.50 (4.75)	-	-	-
Handedness (right:left)		10:0	-	-	-
Disease duration (years)		13.00 (15.87)[a]	-	-	-
Current medication		Antidepressant: clomipramine (n = 10); fluvoxamine (n = 3); fluoxetine (n = 2); venlafaxine (n = 2); paroxetine (n = 1); escitalopram (n = 1); trazodone (n = 1). Antipsychotic: risperidone (n = 2). Antiepileptic: lamotrigine (n = 1); clonazepam (n = 1); gabapentin (n = 1). Anxiolytic: lorazepam (n = 1). Other: docosahexaenoic acid (n = 1).	-	Medication changes (yes:no) 4:5[a]	-
Current psychotherapy (yes:no)		5:5	-	Psychotherapy changes (yes:no) 1:8[a]	-
Y-BOCS	Total	32.50 (10.50)	28.50 (13.25)	31.00 (16.00)[a]	$\chi^2(2) = 2.61$; $p = 0.272$; $KW = 0.83$
	Obsessions	17.00 (4.50)	13.50 (6.50)	14.00 (9.00)[a]	$\chi^2(2) = 7.29$; $p_{bonf} = 0.052$; $KW = 0.80$
	Compulsions	15.00 (6.75)	16.50 (6.25)	14.00 (5.00)[a]	$\chi^2(2) = 1.81$; $p_{bonf} = 0.810$; $KW = 0.83$
OCI-R	**Total**	**38.00 (9.75)**	-	**28.00 (25.00)[a]**	**$W = 36.00$; $p = 0.007$; $RC = 1.00$**
	Washing	10.00 (5.00)	-	8.00 (7.00)[a]	$W = 22.00$; $p_{bonf} = 0.600$; $RC = 0.57$
	Checking	4.50 (6.50)	-	2.00 (10.00)[a]	$W = 30.00$; $p_{bonf} = 0.294$; $RC = 0.67$
	Ordering	3.50 (7.50)	-	4.00 (2.00)[a]	$W = 27.00$; $p_{bonf} = 0.696$; $RC = 0.50$
	Hoarding	2.00 (4.50)	-	2.00 (1.00)[a]	$W = 22.00$; $p_{bonf} = 0.606$; $RC = 0.57$
	Obsessing	8.00 (5.00)	-	6.00 (5.00)[a]	$W = 18.50$; $p_{bonf} = 0.318$; $RC = 0.76$

Table 1 continues in the next page

Table 1 Description of sociodemographic, clinical and psychometric data from the treatment group (n = 10). The statistical differences from the Friedman test among visit 1, 4 and 5 are also represented with Kendall's W (KW) effect size (Wilcoxon test between visit 1 and 5 for the OCI-R and PSS-10 scale with rank-biserial correlation effect size [RC]). Statistically significant values are marked in bold (p_{bonf} Bonferroni correction).

		Visit 1	Visit 4	Visit 5	Statistical results
	Neutralizing	3.50 (3.00)	-	2.00 (7.00)[a]	W = 28.00; p_{bonf} = 0.546; RC = 0.56
	HARS	21.50 (15.25)	8.50 (11.50)	13.00 (8.00)[a]	$\chi^2(2)$ = 4.67; p = 0.092; KW =0.80
STAI	Total	111.50 (34.00)	105.00 (21.50)	102.00 (16.00)[a]	$\chi^2(2)$ = 4.67; p = 0.097; KW =0.81
	State	48.00 (16.25)	48.50 (9.25)	41.00 (7.00)[a]	$\chi^2(2)$ = 5.56; p_{bonf} = 0.124; KW =0.56
	Trait	66.00 (20.50)	58.50 (14.25)	59.00 (18.00)[a]	$\chi^2(2)$ = 6.22; p_{bonf} = 0.090; KW =0.87
	HDRS	16.50 (8.75)	7.50 (9.50)	12.00 (11.00)[a]	$\chi^2(2)$ = 4.17; p = 0.124; KW =0.79
	PSS-10	**28.50 (7.75)**	-	**21.00 (11.00)[a]**	**W = 39.00; p = 0.029; RC =0.73**
ERQ	Cognitive reappraisal	23.50 (20.00)	26.50 (13.25)	23.00 (14.00)[a]	$\chi^2(2)$ = 0.79; p = 0.674; KW =0.86
	Expressive suppression	10.50 (3.50)	12.00 (3.50)	11.00 (4.00)[a]	$\chi^2(2)$ = 0.45; p = 0.798; KW =0.47

[a]One participant with missing data; Data represent median (interquartile range). Y-BOCS - Yale-Brown Obsessive Compulsive Scale; OCI-R - Obsessive-Compulsive Inventory-Revised; STAI - State-Trait Anxiety Inventory; HARS - Hamilton Anxiety Rating Scale; HDRS - Hamilton Anxiety Rating Scale; PSS-10- Perceived Stress Scale; ERQ- Emotion Regulation Questionnaire.

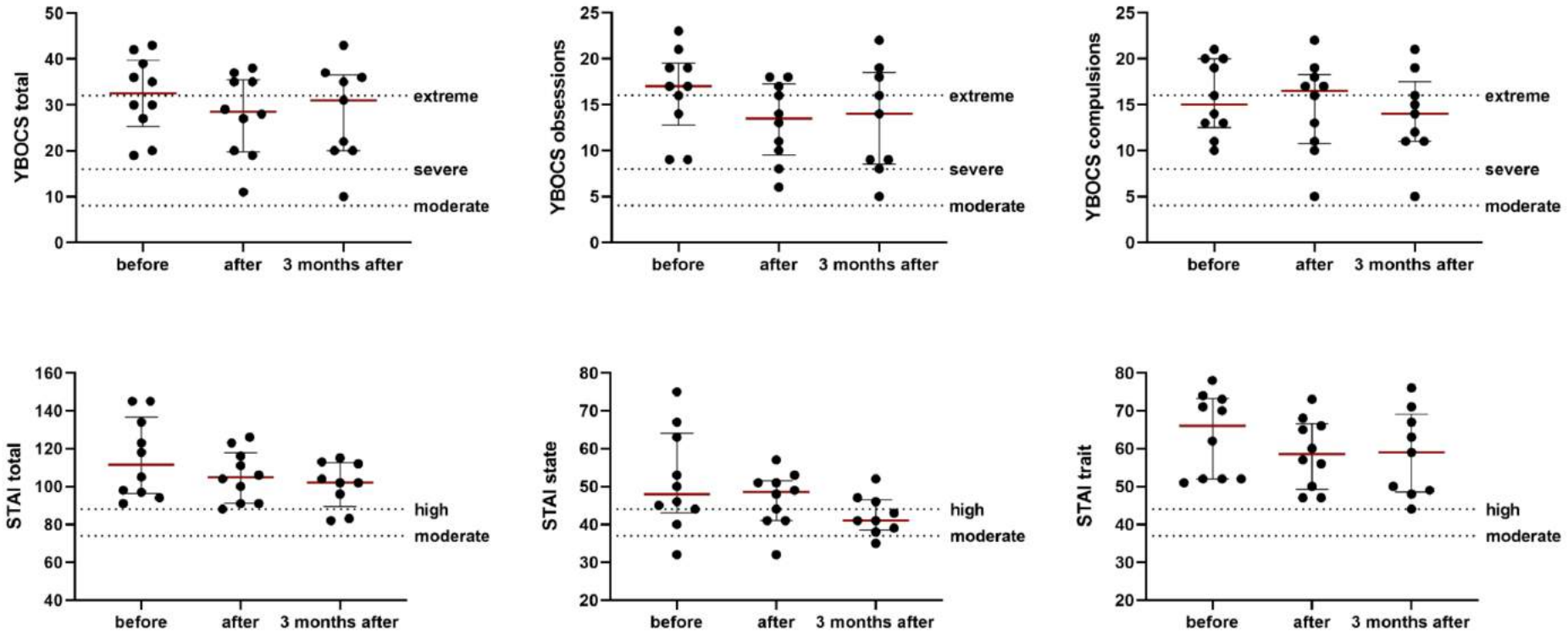


Figure 3 Representation of the variation in the psychometric scales before (visit 1), after (visit 4), and 3 months after (visit 5) neurofeedback (median in red and interquartile range in the whiskers; more information in **Table 1**). YBOCS - Yale-Brown Obsessive Compulsive Scale; STAI - State-Trait Anxiety Inventory.

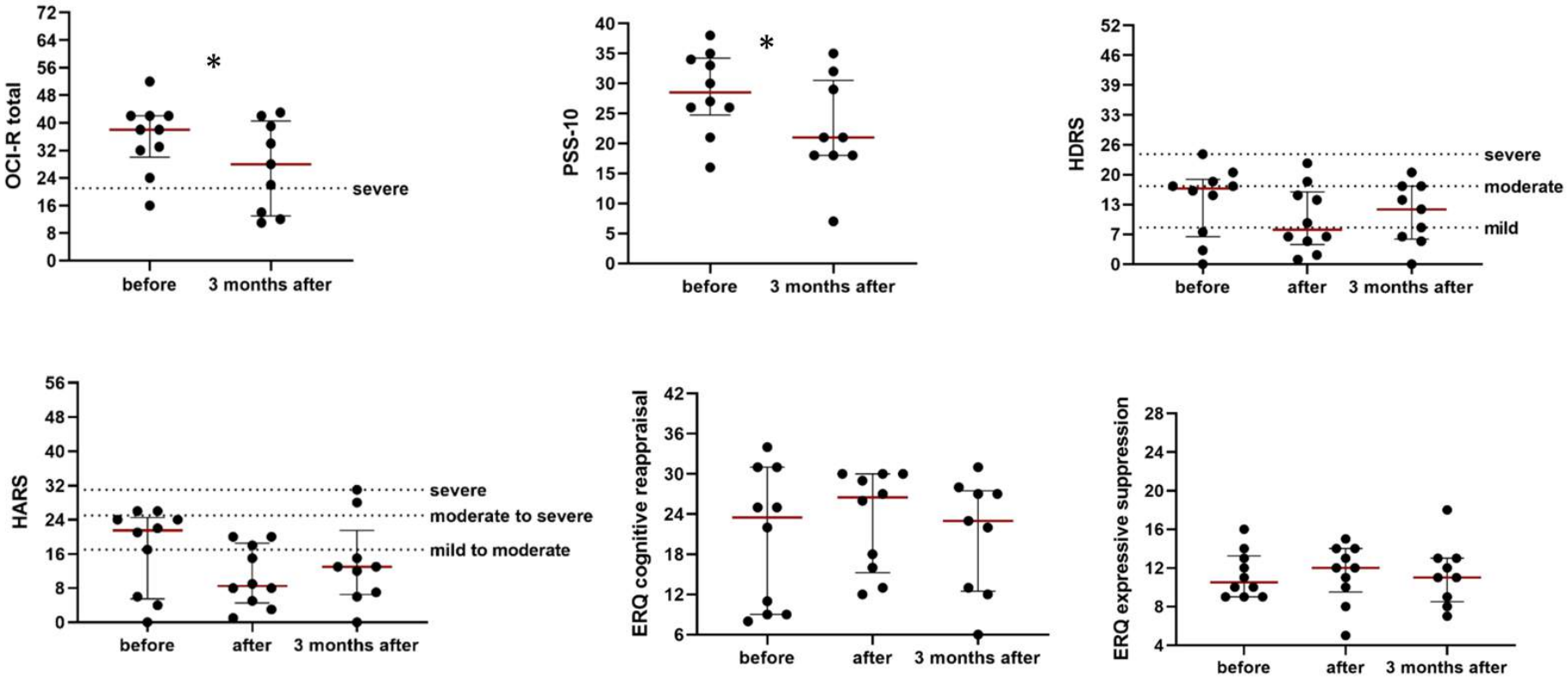


Figure 4 Representation of the variation in the psychometric scales before (visit 1), after (visit 4), and 3 months after (visit 5) neurofeedback (median in red and interquartile range in the whiskers; more information in **Table 1**). *Statistically significant differences; OCI-R - Obsessive-Compulsive Inventory-Revised; PSS-10- Perceived Stress Scale; HDRS - Hamilton Anxiety Rating Scale; HARS - Hamilton Anxiety Rating Scale; ERQ- Emotion Regulation Questionnaire.

e. Resting-state analysis

The ICA analysis allowed the identification of the main resting-state networks: the anterior and posterior salience networks, auditory and language networks, dorsal and ventral default-mode network, basal ganglia network, left and right central executive networks, sensorimotor network, and visual networks (primary visual, higher visual, precuneus, and visuospatial; supplementary **Figure S3**). However, the analysis of differences induced by neurofeedback in the identified resting-state networks did not yield statistically significant results.

The functional connectome (NBS) analysis did not produce statistically significant results.

The analysis of whole-brain FC with the target OFC region (seed-based FC) showed increased negative FC after neurofeedback in a cluster comprising the left middle temporal/ supramarginal/angular gyrus (**Table 3** and **Figure 5**).

f. Exploratory correlations between psychometric measures and brain alterations

We explored if the scale scores changes (HARS, STAI [state, trait and total scores], HDRS, Y-BOCS [obsessions, compulsions and total scores], ERQ [cognitive regulation and expressive suppression scores]) were correlated with the brain activity changes for the localizer stimulus and the FC alterations for the seed-based analysis (Spearman correlation with Bonferroni correction for multiple comparisons). We did not find any statistically significant correlation before applying Bonferroni correction for multiple comparisons.

Table 2 Neurofeedback information from the treatment group (n = 10).

	Session 1			Session 2		
	Run 1	Run2	Run 3	Run 4	Run 5	Run 6
Feedback signal (% OFC change)	-0.08 (0.07)[a]	-0.10 (0.10)[a]	-0.07 (0.08)[a]	-0.05 (0.10)	-0.03 (0.07)	-0.10 (0.10)
Number of sessions	2.00 (0.00)					
Time between sessions (days)	5.00 (2.75)					
Motivation (1 to 9)	7.00 (3.5)			7.00 (3.5)		
Effort (1 to 9)	6.50 (2.00)			7.00 (2.00)		
Sense of success (1 to 9)	5.00 (2.50)			7.00 (3.00)		
Treatment expectation (yes:no)	9:1			9:1		
Neurofeedback belief (yes:no)	6:4			7:3		
Regulation strategies change (yes:no)	8:2			6:4		
Regulation strategies	Distancing (n = 8); reinterpretation (n = 9); relaxation (n = 1)			Distancing (n = 9); reinterpretation (n = 9); relaxation (n = 1)		
Beneficial effects	Better self-control (n = 5); relaxation (n = 1); motivation (n = 1)			Better self-control (n = 4); relaxation (n = 1)		
Adverse effects	Frustration (n = 2); headache (n = 2); tiredness (n = 1)			Frustration (n = 2); headache (n = 1); tiredness (n = 4); disgust (n = 2)		

[a]One participant with missing data due to a data saving error; Data represent median (interquartile range); OFC – orbitofrontal cortex.

Table 3 Description of brain functional statistically significant changes after neurofeedback (*randomise* 0.95 < t < 1.00).

Analysis	Contrast	Brain regions	Size (voxels)	Peak voxel MNI coordinates (mm)
Brain activity induced by localizer stimulus	After > before Imagine > observe	↑ R middle frontal gyrus, precentral gyrus, and postcentral gyrus	8	44 -10 44
Seed-based functional connectivity (FC) at rest (OFC region)	After > before	↑ negative FC L middle temporal gyrus, posterior supramarginal gyrus, angular gyrus, and superior/inferior lateral occipital cortex	12	-56 -56 14

MNI – Montreal Neurological Institute; OFC – orbitofrontal cortex; L – left hemisphere; R – right hemisphere; FC – functional connectivity.

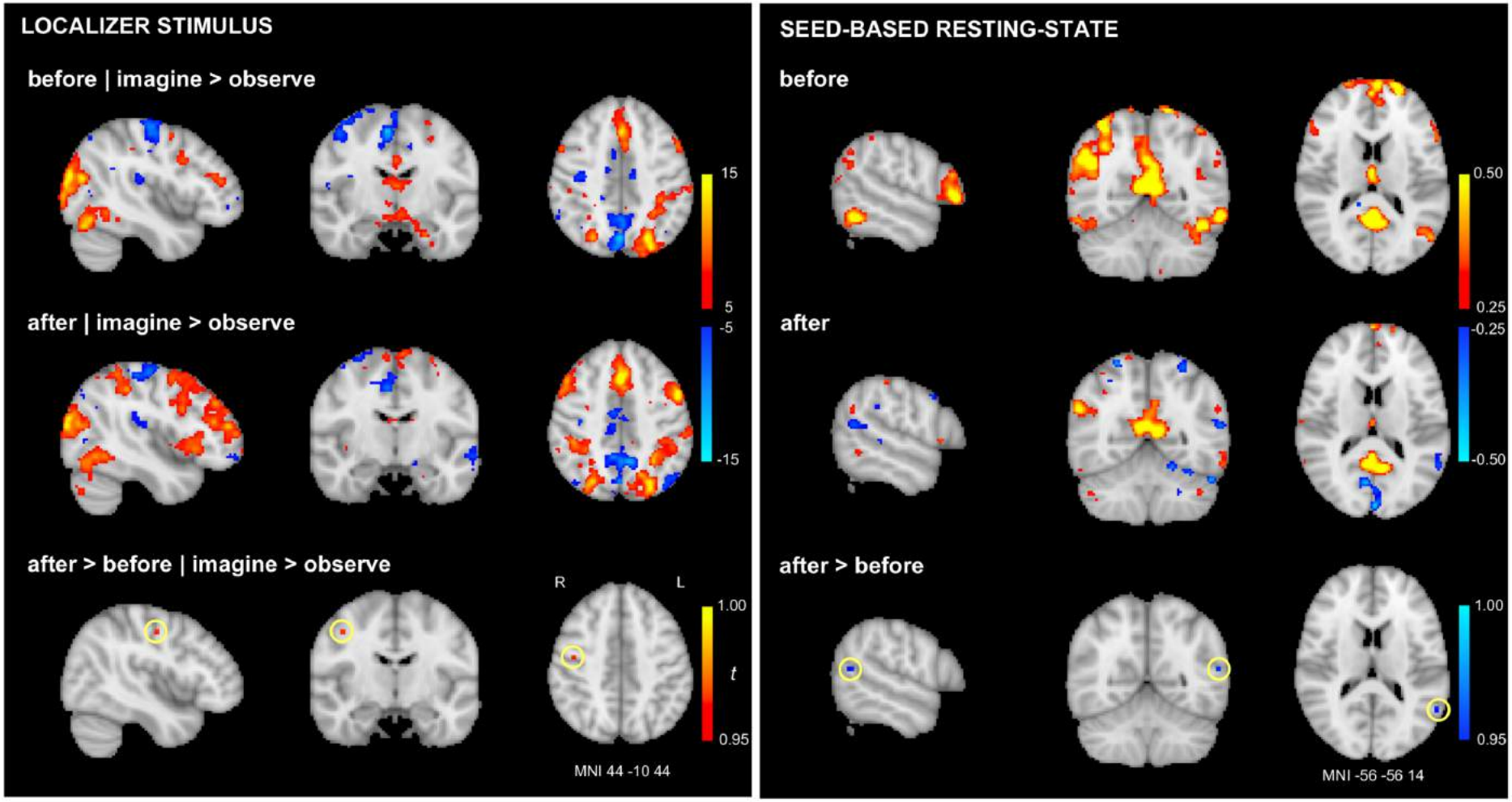


Figure 5 Representation of the brain activity increase for the localizer stimulus (left) and the increased negative functional connectivity for the seed-based analysis with the orbitofrontal cortex (right) after neurofeedback (see **Table 3** for more details). The statistical maps of before and after are not corrected for better visualization. R – right; L – left; MNI - Montreal Neurological Institute (coordinates in mm).

5. Discussion

In this study, we explored the efficacy of fMRI neurofeedback for treatment-resistant OCD patients with primary contamination-related symptoms. Neurofeedback led to a long-term decrease in stress and OCD-related symptoms. One patient responded to the treatment and two patients were partial responders three months after finishing the neurofeedback protocol. Additionally, we observed brain activity alterations during a symptom-provoking task, and functional connectivity changes at rest after the neurofeedback sessions. The brain functional changes were not associated with symptomatic improvement.

One-third of the OCD patients responded partially/fully to the neurofeedback training after three months. The median Y-BOCS score reduction was 12.15 (19.00) % after the neurofeedback sessions and 7.70 (26.70) % three months after treatment. In line with our results, previous neurofeedback studies with non-resistant OCD patients reported decreases in Y-BOCS between 7 and 20 % after two to ten sessions (Buyukturkoglu et al., 2015; Deng et al., 2014; Dustin Scheinost et al., 2014). Nonetheless, the observed Y-BOCS changes are lower compared to previous studies of augmentation drugs in treatment-resistant OCD patients (Y-BOCS decrease between 10 and 26 %), namely anti-psychotics and glutamatergic agents (Carey et al., 2012; Dold et al., 2013; Ipser et al., 2006; Veale et al., 2014; Zhou et al., 2019). However, these studies included mostly patients resistant to at least one SSRI trial while our sample has patients already taking augmentation medication. Moreover, these clinical trials involved daily medication for two to sixteen weeks while our protocol consists of two days of neurofeedback. Thus, prolonged neurofeedback protocols might lead to greater Y-BOCS reductions in treatment-resistant patients. Indeed, EEG neurofeedback studies with more sessions (1 to 2 months) pointed to greater OCD symptomatic improvement (-78 to -52 %), including protocols with treatment-resistant patients (Deng et al., 2014; Koprivová et al., 2013; Sürmeli & Ertem, 2011).

Despite the absence of statistically significant changes in Y-BOCS after three months, we observed a significant decrease in the OCI-R score in line with past reports of long-term effects of neurofeedback in OCD-related symptoms (Rance et al., 2018; Sürmeli & Ertem, 2011). Additionally, we observed a significant reduction in self-perceived stress after three months. Stress might induce or enhance OCD symptomatology (Adams et al., 2018; S. McLaren & Crowe, 2003), and OCD symptoms are positively associated with perceived stress levels (P. Morgado et al., 2013). In line with our results, both stress and OCD-symptoms decreased after applying yogic techniques with OCD individuals (Shannahoff-Khalsa et al., 1999; Shannahoff-khalsa & Beckett, 1996).

Our results also showed enhanced brain activity in the right middle frontal/precentral, gyrus region after neurofeedback while the participants experienced the contamination versus the neutral pictures (localizer stimulus). Other authors demonstrated reduced activity in orbitofrontal, anterior cingulate, caudate, and thalamic regions after treatment during symptom provocation tasks (Baioui et al., 2013; Bhikram et al., 2016; Morgiève et al., 2014; Nakao et al., 2005, 2014; Schiepek et al., 2013; A. L. Thorsen et al., 2015). Thus, neural activity changes corresponding to symptomatic manifestation after neurofeedback might differ from the ones observed with first-line treatments. Indeed, Buyukturkoglu and colleagues (2015) detected increased responses in the precentral gyrus during neurofeedback. Thus, these dorsolateral prefrontal/premotor regions might be involved in the control exerted during neurofeedback as recently demonstrated by a meta-analysis (Emmert et al., 2016). The patients in our study might have transferred the strategies applied during the neurofeedback sessions while observing the contamination pictures. Nonetheless, the contamination picture ratings did not decrease after neurofeedback.

After neurofeedback, we observed increased negative FC between the OFC region target during neurofeedback and the left temporal/supramarginal/angular gyrus region. Previous authors found resting-state changes after OFC-based neurofeedback in participants with contamination anxiety, namely decreased FC in emotion processing regions (e.g. fusiform and temporal regions) and increased connectivity in lateral prefrontal areas responsible for emotional control (D Scheinost et al., 2013). Past studies demonstrated brain alterations after CBT in correlation with symptomatic improvement, mainly FC decrease in the dorsolateral prefrontal cortex (P. Li et al., 2018; Yang et al., 2015), precentral and temporal gyrus (Moody et al., 2017; Zhao et al., 2017), and occipital cortex (P. Li et al., 2018; Moody et al., 2017; Zhao et al., 2017). The authors proposed that symptomatic improvement after CBT is associated with better control of motor behaviors and cognition. Thus, reduced FC in temporal regions has been observed after neurofeedback (D Scheinost et al., 2013) and cognitive therapy (Zhao et al., 2017) in OCD patients. Other authors also found that alpha and beta power at rest in the middle temporal gyrus is predictive of Y-BOCS changes after neurofeedback (Koprivová et al., 2013). Tian et al. (2016) demonstrated augmented FC strength in orbitofrontal, middle temporal, supramarginal, and lateral occipital regions in treatment-naïve patients (Tian et al., 2016). Thus, the observed increased in negative FC between the orbitofrontal and temporoparietal regions in our study might be related to a better control over obsessions. Although we did not find any correlation between FC changes and symptomatic alterations, we observed a marginal reduction of the obsessions score immediately after the

neurofeedback sessions. However, we need to further confirm this hypothesis with a larger sample of patients.

a. Limitations

Our results need further validation with the sham group to rule out putative confounding variables such as changes in the usual treatment and placebo effects. Given that neurofeedback is not approved as a treatment for OCD, we cannot deprive the patients of their first-line treatment for ethical reasons. Thus, changes in first-line treatment during the implementation of the protocol might have affected the results. We did not meet the predetermined sample size, but our sample was in line with previous neurofeedback studies (Arns et al., 2017; Stoeckel et al., 2014; Thibault et al., 2018). Our results are limited to OCD patients with primary contamination/cleaning symptoms. The putative unblinding of the main outcome raters might have affected the results. Given the limited number of pictures and to avoid habituation effects, the contamination pictures used during neurofeedback were not selected according to participants' specific obsessions/compulsions domain. Thus, these pictures might influence the OFC activity differently for each patient before neurofeedback down-regulation.

b. Conclusions

Our study provides evidence of the long-term effects of fMRI neurofeedback in stress and obsessive-compulsive symptoms in treatment-resistant patients. Additionally, the observed increase in negative FC between prefrontal-temporoparietal regions might underly better control over obsessions after neurofeedback. However, only one-third of the patients responded to neurofeedback training. Longer neurofeedback protocols might yield better symptomatic improvement. Given the elevated costs of fMRI, functional near-infrared spectroscopy is a suitable alternative for neurofeedback approaches (Kohl et al., n.d.; K. Li et al., 2019). Neurofeedback is a promising technique for treatment-resistant OCD, but our results need to be validated with the sham control group.

6. Funding

This work has been funded by National funds, through the Foundation for Science and Technology (FCT)

- project UIDB/50026/2020 and UIDP/50026/2020; and by the projects NORTE-01-0145-FEDER-000013 and NORTE-01-0145-FEDER-000023, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). This work was additionally supported by a research grant from the Clinical Academic Center, Braga, Portugal ("Treating refractory obsessive-compulsive disorder using real-time functional magnetic resonance imaging neurofeedback"). SF was supported by a combined Ph. D. scholarship from FCT and the company iCognitus4ALL - IT Solutions, Lda (PD/BDE/127839/2016). RM was supported by the combined FCT and Enlightenment, Lda fellowship (PDE/BDE/113604/2015) from the PhDiHES program. MPP was supported by a post-doctoral fellowship from institutional funds (EMED_BPD_2019_002). RV was supported by an FCT research fellowship (UMINHO/BI/340/2018).

7. Acknowledgments

We would like to thank Carlos Portugal-Nunes and Celina Gomes for the help with the project implementation. We appreciate the help of Joana Reis with the resting-state analysis. We are thankful to Dr. Daniela Simon, Dr. David Mataix-Cols, Dr. Michelle Hampson, and Dr. Mariela Rance for their contribution to the contamination picture datasets. We appreciate the help of Dr. Yury Koush with the implementation of the OpenNFT software.

8. References

Abramowitz, J. S., & Deacon, B. J. (2006). Psychometric properties and construct validity of the Obsessive–Compulsive Inventory—Revised: Replication and extension with a clinical sample. Journal of Anxiety Disorders, 20(8), 1016–1035. https://doi.org/10.1016/J.JANXDIS.2006.03.001

Adams, T. G., Kelmendi, B., Brake, C. A., Gruner, P., Badour, C. L., & Pittenger, C. (2018). The Role of Stress in the Pathogenesis and Maintenance of Obsessive-Compulsive Disorder. Chronic Stress, 2(1), 247054701875804. https://doi.org/10.1177/2470547018758043

American Psychiatric Association. (2013). Diagnostic Statistical Manual of Mental Disorders (DSM-5). In American Psychiatric Association (5th, revised ed.). American Psychiatric Association Pub, 2013.

Aranyi, G., Cavazza, M., & Charles, F. (2015). Using fNIRS for Prefrontal-Asymmetry Neurofeedback: Methods and Challenges (pp. 7–20). Springer, Cham. https://doi.org/10.1007/978-3-319-24917-9_2

Aranyi, G., Charles, F., & Cavazza, M. (2015). Anger-based BCI Using fNIRS Neurofeedback. Proceedings of the 28th Annual ACM Symposium on User Interface Software & Technology - UIST '15, 511–521. https://doi.org/10.1145/2807442.2807447

Arns, M., Batail, J.-M., Bioulac, S., Congedo, M., Daudet, C., Drapier, D., Fovet, T., Jardri, R., Le-Van-Quyen, M., Lotte, F., Mehler, D., Micoulaud-Franchi, J.-A., Purper-Ouakil, D., & Vialatte, F. (2017). Neurofeedback: One of today's techniques in psychiatry? L'Encéphale, 43(2), 135–145. https://doi.org/10.1016/j.encep.2016.11.003

Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Medical Image Analysis, 12(1), 26–41. https://doi.org/10.1016/j.media.2007.06.004

Baioui, A., Pilgramm, J., Kagerer, S., Walter, B., Vaitl, D., & Stark, R. (2013). Neural correlates of symptom reduction after CBT in obsessive-compulsive washers—An fMRI symptom provocation study. Journal of Obsessive-Compulsive and Related Disorders, 2(3), 322–330. https://doi.org/10.1016/j.jocrd.2013.04.006

Barzegary, L., Yaghubi, H., & Rostami, R. (2011). The effect of QEEG- guided neurofeedback treatment in decreasing of OCD symptoms. Procedia - Social and Behavioral Sciences, 30, 2659–2662. https://doi.org/10.1016/j.sbspro.2011.10.519

Beckmann, C., Mackay, C., Filippini, N., & Smith, S. (2009). Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. NeuroImage, 47, S148. https://doi.org/10.1016/S1053-8119(09)71511-3

Beckmann, C.F., & Smith, S. M. (2004). Probabilistic Independent Component Analysis for Functional Magnetic Resonance Imaging. IEEE Transactions on Medical Imaging, 23(2), 137–152. https://doi.org/10.1109/TMI.2003.822821

Beckmann, Christian F. (2012). Modelling with independent components. NeuroImage, 62(2), 891–901. https://doi.org/10.1016/j.neuroimage.2012.02.020

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage, 37(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Bhikram, T. P., Farb, N. A. S., Ravindran, L. N., Papadopoulos, Y. G., Conn, D. K., Pollock, B. G., & Ravindran, A. V. (2016). The Effect of Intravenous Citalopram on the Neural Substrates of Obsessive-Compulsive Disorder. The Journal of Neuropsychiatry and Clinical Neurosciences, 28(3), 243–247. https://doi.org/10.1176/appi.neuropsych.15090213

Brakoulias, V., Starcevic, V., Albert, U., Arumugham, S. S., Bailey, B. E., Belloch, A., Borda, T., Dell'Osso, L., Elias, J. A., Falkenstein, M. J., Ferrao, Y. A., Fontenelle, L. F., Jelinek, L., Kalogeraki, L., Kay, B., Laurito, L. D., Lochner, C., Maina, G., Marazziti, D., … Fineberg, N. A. (2019). Treatments used for obsessive-compulsive disorder-An international perspective. Human Psychopharmacology: Clinical and Experimental, December 2018, e2686. https://doi.org/10.1002/hup.2686

Bruin, W., Denys, D., & van Wingen, G. (2019). Diagnostic neuroimaging markers of obsessive-compulsive disorder: Initial evidence from structural and functional MRI studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 91(July 2018), 49–59. https://doi.org/10.1016/j.pnpbp.2018.08.005

Burchi, E., Hollander, E., & Pallanti, S. (2018). From Treatment Response to Recovery: A Realistic Goal in OCD. International Journal of Neuropsychopharmacology, 21(11), 1007–1013. https://doi.org/10.1093/ijnp/pyy079

Buyukturkoglu, K., Roettgers, H., Sommer, J., Rana, M., Dietzsch, L., Arikan, E. B., Veit, R., Malekshahi, R., Kircher, T., Birbaumer, N., Sitaram, R., & Ruiz, S. (2015). Self-Regulation of Anterior Insula with Real-

Time fMRI and Its Behavioral Effects in Obsessive-Compulsive Disorder: A Feasibility Study. PLOS ONE, 10(8), e0135872. https://doi.org/10.1371/journal.pone.0135872

Carey, P. D., Lochner, C., Kidd, M., Van Ameringen, M., Stein, D. J., & Denys, D. (2012). Quetiapine augmentation of serotonin reuptake inhibitors in treatment-refractory obsessive–compulsive disorder. International Clinical Psychopharmacology, 27(6), 1. https://doi.org/10.1097/YIC.0b013e3283576881

Castro-Rodrigues, P., Camacho, M., Almeida, S., Marinho, M., Soares, C., Barahona-Corrêa, J. B., & Oliveira-Maia, A. J. (2018). Criterion Validity of the Yale-Brown Obsessive-Compulsive Scale Second Edition for Diagnosis of Obsessive-Compulsive Disorder in Adults. Frontiers in Psychiatry, 9(SEP), 1–10. https://doi.org/10.3389/fpsyt.2018.00431

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A Global Measure of Perceived Stress. Journal of Health and Social Behavior, 24(4), 385. https://doi.org/10.2307/2136404

Cox, R. W. (1996). AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. Computers and Biomedical Research, 29(3), 162–173. https://doi.org/10.1006/cbmr.1996.0014

D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nature Reviews Neuroscience, 4(11), 863–872. https://doi.org/10.1038/nrn1246

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical Surface-Based Analysis. NeuroImage, 9(2), 179–194. https://doi.org/10.1006/nimg.1998.0395

Deng, X., Wang, G., Zhou, L., Zhang, X., Yang, M., Han, G., Tu, Z., & Liu, B. (2014). Randomized controlled trial of adjunctive EEG-biofeedback treatment of obsessive-compulsive disorder. Shanghai Archives of Psychiatry, 26(5), 272–279. https://doi.org/10.11919/j.issn.1002-0829.214067

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage, 31(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Dold, M., Aigner, M., Lanzenberger, R., & Kasper, S. (2013). Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. International Journal of Neuropsychopharmacology, 16(3), 557–574. https://doi.org/10.1017/S1461145712000740

Emmert, K., Kopel, R., Sulzer, J., Brühl, A. B., Berman, B. D., Linden, D. E. J., Horovitz, S. G., Breimhorst, M., Caria, A., Frank, S., Johnston, S., Long, Z., Paret, C., Robineau, F., Veit, R., Bartsch, A., Beckmann, C. F., Van De Ville, D., & Haller, S. (2016). Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated? NeuroImage, 124, 806–812. https://doi.org/10.1016/j.neuroimage.2015.09.042

Esteban, O., Ciric, R., Finc, K., Blair, R., Markiewicz, C. J., Moodie, C. A., Kent, J. D., Goncalves, M., DuPre, E., Gomez, D. E. P., Ye, Z., Salo, T., Valabregue, R., Amlien, I. K., Liem, F., Jacoby, N., Stojić, H., Cieslak, M., Urchs, S., … Gorgolewski, K. J. (2019). Analysis of task-based functional MRI data preprocessed with fMRIPrep. BioRxiv, 694364. https://doi.org/10.1101/694364

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski,

K. J. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. Nature Methods, 16(1), 111–116. https://doi.org/10.1038/s41592-018-0235-4

Feinberg, D. A., Moeller, S., Smith, S. M., Auerbach, E., Ramanna, S., Glasser, M. F., Miller, K. L., Ugurbil, K., & Yacoub, E. (2010). Multiplexed Echo Planar Imaging for Sub-Second Whole Brain FMRI and Fast Diffusion Imaging. PLoS ONE, 5(12), e15710. https://doi.org/10.1371/journal.pone.0015710

Ferreira, S., Pêgo, J. M., & Morgado, P. (2019). The efficacy of biofeedback approaches for obsessive-compulsive and related disorders: A systematic review and meta-analysis. Psychiatry Research, 272(December 2018), 237–245. https://doi.org/10.1016/j.psychres.2018.12.096

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. Psychological Assessment, 14(4), 485–496. https://doi.org/10.1037/1040-3590.14.4.485

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. NeuroImage, 54(1), 313–327. https://doi.org/10.1016/j.neuroimage.2010.07.033

Fornaro, M. (2019). Choosing the appropriate pharmacotherapy for obsessive-compulsive disorder in adult patients with comorbid anxiety disorders: clinical and nosological considerations. Expert Opinion on Pharmacotherapy, 20(2), 123–126. https://doi.org/10.1080/14656566.2018.1549225

Frydman, I., de Salles Andrade, J. B., Vigne, P., & Fontenelle, L. F. (2016). Can Neuroimaging Provide Reliable Biomarkers for Obsessive-Compulsive Disorder? A Narrative Review. Current Psychiatry Reports, 18(10), 90. https://doi.org/10.1007/s11920-016-0729-7

Garrison, K. A., Santoyo, J. F., Davis, J. H., Thornhill, T. A., Kerr, C. E., & Brewer, J. A. (2013). Effortless awareness: using real time neurofeedback to investigate correlates of posterior cingulate cortex activity in meditators' self-report. Frontiers in Human Neuroscience, 7(August), 1–9. https://doi.org/10.3389/fnhum.2013.00440

Gershkovich, M., Wheaton, M. G., & Simpson, H. B. (2017). Management of Treatment-Resistant Obsessive-Compulsive Disorder. Current Treatment Options in Psychiatry, 4(4), 357–370. https://doi.org/10.1007/s40501-017-0127-8

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J. R., Van Essen, D. C., & Jenkinson, M. (2013). The minimal preprocessing pipelines for the Human Connectome Project. NeuroImage, 80, 105–124. https://doi.org/10.1016/j.neuroimage.2013.04.127

Gonçalves, Ó. F., Carvalho, S., Leite, J., Fernandes-Gonçalves, A., Carracedo, A., & Sampaio, A. (2016). Cognitive and emotional impairments in obsessive–compulsive disorder: Evidence from functional brain alterations. Porto Biomedical Journal, 1(3), 92–105. https://doi.org/10.1016/j.pbj.2016.07.005

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. II. Validity. Archives of General Psychiatry, 46(11), 1012–1016. http://www.ncbi.nlm.nih.gov/pubmed/2510699

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Archives of General Psychiatry, 46(11), 1006–1011. http://www.ncbi.nlm.nih.gov/pubmed/2684084

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. NeuroImage, 48(1), 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. Journal of Personality and Social Psychology, 85(2), 348–362. http://www.ncbi.nlm.nih.gov/pubmed/12916575

Gürsel, D. A., Avram, M., Sorg, C., Brandl, F., & Koch, K. (2018). Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. Neuroscience & Biobehavioral Reviews, 87(October 2017), 151–160. https://doi.org/10.1016/j.neubiorev.2018.01.016

Hamilton, M. (1959). The assessment of anxiety states by rating. The British Journal of Medical Psychology, 32(1), 50–55. http://www.ncbi.nlm.nih.gov/pubmed/13638508

Hamilton, M. (1960). A rating scale for depression. Journal of Neurology, Neurosurgery & Psychiatry, 23(1), 56–62. https://doi.org/10.1136/jnnp.23.1.56

Hammond, D. Corydon. (2003). QEEG-Guided Neurofeedback in the Treatment of Obsessive Compulsive Disorder. Journal of Neurotherapy, 7(2), 25–52. https://doi.org/10.1300/J184v07n02_03

Hammond, D C. (2004). Treatment of the obsessional subtype of obsessive compulsive disorder with neurofeedback. Biofeedback, 32(December 2016), 9–12. https://www.researchgate.net/publication/284832012_Treatment_of_the_obsessional_subtype_of_obsessive_compulsive_disorder_with_neurofeedback

Hampson, M., Stoica, T., Saksa, J., Scheinost, D., Qiu, M., Bhawnani, J., Pittenger, C., Papademetris, X., & Constable, T. (2012). Real-time fMRI Biofeedback Targeting the Orbitofrontal Cortex for Contamination Anxiety. Journal of Visualized Experiments, 59. https://doi.org/10.3791/3535

Hirschtritt, M. E., Bloch, M. H., & Mathews, C. A. (2017). Obsessive-Compulsive Disorder Advances in Diagnosis and Treatment. JAMA, 317(13), 1358. https://doi.org/10.1001/jama.2017.2200

Horowitz-Kraus, T., DiFrancesco, M., Kay, B., Wang, Y., & Holland, S. K. (2015). Increased resting-state functional connectivity of visual- and cognitive-control brain networks after training in children with reading difficulties. NeuroImage: Clinical, 8, 619–630. https://doi.org/10.1016/j.nicl.2015.06.010

Ipser, J. C., Carey, P., Dhansay, Y., Fakier, N., Seedat, S., & Stein, D. J. (2006). Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database of Systematic Reviews, 4. https://doi.org/10.1002/14651858.CD005473.pub2

J.H. Begemann, M., J.R. Florisse, E., van Lutterveld, R., Kooyman, M., & E. Sommer, I. (2016). Efficacy of EEG neurofeedback in psychiatry: A comprehensive overview and meta-analysis. Translational Brain Rhythmicity, 1(1), 19–29. https://doi.org/10.15761/TBR.1000105

Jenkinson, M. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. NeuroImage, 17(2), 825–841. https://doi.org/10.1016/S1053-8119(02)91132-8

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. NeuroImage, 62(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jiang, Y., Abiri, R., & Zhao, X. (2017). Tuning Up the Old Brain with New Tricks: Attention Training via Neurofeedback. Frontiers in Aging Neuroscience, 9, 52. https://doi.org/10.3389/fnagi.2017.00052

Klein, A., Ghosh, S. S., Bao, F. S., Giard, J., Häme, Y., Stavsky, E., Lee, N., Rossa, B., Reuter, M., Chaibub Neto, E., & Keshavan, A. (2017). Mindboggling morphometry of human brains. PLOS Computational Biology, 13(2), e1005350. https://doi.org/10.1371/journal.pcbi.1005350

Kohl, S. H., Mehler, D. M. A., Thibault, R. T., Sorger, B., Section, C. N., Faculty, M., V, B. I. B., Kingdom, U., & Kingdom, U. (n.d.). The potential of functional near-infrared spectroscopy-based neurofeedback for modulating brain functions – a systematic review.

Koprivová, J., Congedo, M., Raszka, M., Praško, J., Brunovský, M., Horácek, J., Kopřivová, J., Congedo, M., Raszka, M., Praško, J., Brunovský, M., Horáček, J., Koprivová, J., Congedo, M., Raszka, M., Praško, J., Brunovský, M., & Horácek, J. (2013). Prediction of Treatment Response and the Effect of Independent Component Neurofeedback in Obsessive-Compulsive Disorder: A Randomized, Sham-Controlled, Double-Blind Study. Neuropsychobiology, 67(4), 210–223. https://doi.org/10.1159/000347087

Koush, Y., Ashburner, J., Prilepin, E., Sladky, R., Zeidman, P., Bibikov, S., Scharnowski, F., Nikonorov, A., & De Ville, D. Van. (2017). OpenNFT: An open-source Python/Matlab framework for real-time fMRI neurofeedback training based on activity, connectivity and multivariate pattern analysis. NeuroImage, 156, 489–503. https://doi.org/10.1016/j.neuroimage.2017.06.039

Koush, Y., Ashburner, J., Prilepin, E., Sladky, R., Zeidman, P., Bibikov, S., Scharnowski, F., Nikonorov, A., & Van De Ville, D. (2017). Real-time fMRI data for testing OpenNFT functionality. Data in Brief, 14, 344–347. https://doi.org/10.1016/j.dib.2017.07.049

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). International Affective Picture System (IAPS): Technical Manual and Affective Ratings. NIMH Center for the Study of Emotion and Attention, 39–58. https://doi.org/10.1027/0269-8803/a000147

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2005). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-6.

Li, K., Jiang, Y., Gong, Y., Zhao, W., Zhao, Z., Liu, X., Kendrick, K. M., Zhu, C., & Becker, B. (2019). Functional near-infrared spectroscopy-informed neurofeedback: regional-specific modulation of lateral orbitofrontal activation and cognitive flexibility. Neurophotonics, 6(02), 1. https://doi.org/10.1117/1.NPh.6.2.025011

Li, P., Yang, X., Greenshaw, A. J., Li, S., Luo, J., Han, H., Liu, J., Zhong, Z., Guo, Z., Xiong, H., Yao, S., Chen, Y., Sun, J., & Li, Z. (2018). The effects of cognitive behavioral therapy on resting-state functional brain network in drug-naive patients with obsessive-compulsive disorder. Brain and Behavior, 8(5), e00963. https://doi.org/10.1002/brb3.963

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. NeuroImage, 193(March), 75–92. https://doi.org/10.1016/j.neuroimage.2019.03.011

Lubianiker, N., Goldway, N., Fruchtman-Steinbok, T., Paret, C., Keynan, J. N., Singer, N., Cohen, A., Kadosh, K. C., Linden, D. E. J., & Hendler, T. (2019). Process-based framework for precise neuromodulation. Nature Human Behaviour, 3(5), 436–445. https://doi.org/10.1038/s41562-019-0573-y

MacNamara, A., DiGangi, J., & Phan, K. L. (2016). Aberrant Spontaneous and Task-Dependent Functional Connections in the Anxious Brain. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1(3), 278–287. https://doi.org/10.1016/j.bpsc.2015.12.004

Mataix-Cols, D., de la Cruz, L. F., Nordsletten, A. E., Lenhard, F., Isomura, K., & Simpson, H. B. (2016). Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder. World Psychiatry, 15(1), 80–81. https://doi.org/10.1002/wps.20299

Mataix-Cols, D., Lawrence, N. S., Wooderson, S., Speckens, A., & Phillips, M. L. (2009). The Maudsley Obsessive–Compulsive Stimuli Set: Validation of a standardized paradigm for symptom-specific provocation in obsessive–compulsive disorder. Psychiatry Research, 168(3), 238–241. https://doi.org/10.1016/j.psychres.2008.05.007

McLaren, S., & Crowe, S. F. (2003). The contribution of perceived control of stressful life events and thought suppression to the symptoms of obsessive–compulsive disorder in both non-clinical and clinical samples. Journal of Anxiety Disorders, 17(4), 389–403. https://doi.org/10.1016/S0887-6185(02)00224-4

Meir-Hasson, Y., Kinreich, S., Podlipsky, I., Hendler, T., & Intrator, N. (2014). An EEG Finger-Print of fMRI deep regional activation. NeuroImage, 102(P1), 128–141. https://doi.org/10.1016/j.neuroimage.2013.11.004

Mel'nikov, M. E., Shtark, M. B., Savelov, A. A., & Bruhl, A. (2018). Biocontrol Using fMRI Signals Recorded in Real Time: A New-Generation Neurotherapy. Neuroscience and Behavioral Physiology, 48(3), 295–316. https://doi.org/10.1007/s11055-018-0563-y

Micoulaud-Franchi, J.-A., McGonigal, A., Lopez, R., Daudet, C., Kotwas, I., & Bartolomei, F. (2015). Electroencephalographic neurofeedback: Level of evidence in mental and brain disorders and suggestions for good clinical practice. Neurophysiologie Clinique/Clinical Neurophysiology, 45(6), 423–433. https://doi.org/10.1016/j.neucli.2015.10.077

Moeller, S., Yacoub, E., Olman, C. A., Auerbach, E., Strupp, J., Harel, N., & Uğurbil, K. (2010). Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial parallel imaging with application to high spatial and temporal whole-brain fMRI. Magnetic Resonance in Medicine, 63(5), 1144–1153. https://doi.org/10.1002/mrm.22361

Moody, T. D., Morfini, F., Cheng, G., Sheen, C., Tadayonnejad, R., Reggente, N., O'Neill, J., & Feusner, J. D. (2017). Mechanisms of cognitive-behavioral therapy for obsessive-compulsive disorder involve robust and extensive increases in brain network connectivity. Translational Psychiatry, 7(9), e1230–e1230. https://doi.org/10.1038/tp.2017.192

Moreira, P. S., Marques, P., Soriano-Mas, C., Magalhães, R., Sousa, N., Soares, J. M., & Morgado, P. (2017). The neural correlates of obsessive-compulsive disorder: a multimodal perspective. Translational Psychiatry, 7(8), e1224. https://doi.org/10.1038/tp.2017.189

Morgado, P., Freitas, D., Bessa, J. M., Sousa, N., & Cerqueira, J. J. (2013). Perceived Stress in Obsessive–Compulsive Disorder is Related with Obsessive but Not Compulsive Symptoms. Frontiers in Psychiatry, 4(APR), 21. https://doi.org/10.3389/fpsyt.2013.00021

Morgiève, M., N'Diaye, K., Haynes, W. I. A., Granger, B., Clair, A.-H., Pelissolo, A., & Mallet, L. (2014). Dynamics of psychotherapy-related cerebral haemodynamic changes in obsessive compulsive disorder using a personalized exposure task in functional magnetic resonance imaging. Psychological Medicine, 44(7), 1461–1473. https://doi.org/10.1017/S0033291713002237

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatani, E., Nabeyama, M., Yoshizato, C., Kudoh, A., Tada, K., Yoshioka, K., Kawamoto, M., Togao, O., & Kanba, S. (2005). Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: A functional magnetic resonance imaging study. Biological Psychiatry, 57(8), 901–910. https://doi.org/10.1016/j.biopsych.2004.12.039

Nakao, T., Okada, K., & Kanba, S. (2014). Neurobiological model of obsessive-compulsive disorder: Evidence from recent neuropsychological and neuroimaging findings. Psychiatry and Clinical Neurosciences, 68(8), 587–605. https://doi.org/10.1111/pcn.12195

Nickerson, L. D., Smith, S. M., Öngür, D., & Beckmann, C. F. (2017). Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. Frontiers in Neuroscience, 11(MAR). https://doi.org/10.3389/fnins.2017.00115

Pearcy, C. P., Anderson, R. A., Egan, S. J., & Rees, C. S. (2016). A systematic review and meta-analysis of self-help therapeutic interventions for obsessive–compulsive disorder: Is therapeutic contact key to overall improvement? Journal of Behavior Therapy and Experimental Psychiatry, 51, 74–83. https://doi.org/10.1016/j.jbtep.2015.12.007

Peirce, J. W. (2007). PsychoPy—Psychophysics software in Python. Journal of Neuroscience Methods, 162(1–2), 8–13. https://doi.org/10.1016/j.jneumeth.2006.11.017

Peirce, J. W. (2008). Generating stimuli for neuroscience using PsychoPy. Frontiers in Neuroinformatics, 2, 10. https://doi.org/10.3389/neuro.11.010.2008

Picó-Pérez, M., Moreira, P. S., Ferreira, V. D. M., Radua, J., Mataix-Cols, D., Sousa, N., Soriano-Mas, C., & Morgado, P. (2020). Modality-specific overlaps in brain structure and function in Obsessive-compulsive disorder: multimodal meta-analysis of case-control MRI studies. Neuroscience & Biobehavioral Reviews. https://doi.org/10.1016/j.neubiorev.2020.01.033

Picó-Pérez, M., Radua, J., Steward, T., Menchón, J. M., & Soriano-Mas, C. (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 79(January), 96–104. https://doi.org/10.1016/j.pnpbp.2017.06.001

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage, 59(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2013). Steps toward optimizing motion artifact removal in functional connectivity MRI; a reply to Carp. NeuroImage, 76(1), 439–441. https://doi.org/10.1016/j.neuroimage.2012.03.017

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage, 84, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Powers, J. P., & LaBar, K. S. (2019). Regulating emotion through distancing: A taxonomy, neurocognitive model, and supporting meta-analysis. Neuroscience & Biobehavioral Reviews, 96(January 2018), 155–173. https://doi.org/10.1016/j.neubiorev.2018.04.023

Rachid, F. (2019). Transcranial direct current stimulation for the treatment of obsessive-compulsive disorder? A qualitative review of safety and efficacy. Psychiatry Research, 271(October 2018), 259–264. https://doi.org/10.1016/j.psychres.2018.11.033

Radua, J., Stoica, T., Scheinost, D., Pittenger, C., & Hampson, M. (2018). Neural Correlates of Success and Failure Signals During Neurofeedback Learning. Neuroscience, 378, 11–21. https://doi.org/10.1016/j.neuroscience.2016.04.003

Rance, M., Walsh, C., Sukhodolsky, D. G., Pittman, B., Qiu, M., Kichuk, S. A., Wasylink, S., Koller, W. N., Bloch, M., Gruner, P., Scheinost, D., Pittenger, C., & Hampson, M. (2018). Time course of clinical change following neurofeedback. NeuroImage. https://doi.org/10.1016/j.neuroimage.2018.05.001

Randell, E., McNamara, R., Subramanian, L., Hood, K., & Linden, D. (2018). Current practices in clinical neurofeedback with functional MRI—Analysis of a survey using the TIDieR checklist. European Psychiatry, 50, 28–33. https://doi.org/10.1016/j.eurpsy.2017.10.011

Scheinost, D, Stoica, T., Saksa, J., Papademetris, X., Constable, R. T., Pittenger, C., & Hampson, M. (2013). Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity. Translational Psychiatry, 3(4), e250. https://doi.org/10.1038/tp.2013.24

Scheinost, Dustin, Stoica, T., Wasylink, S., Gruner, P., Saksa, J., Pittenger, C., & Hampson, M. (2014). Resting state functional connectivity predicts neurofeedback response. Frontiers in Behavioral Neuroscience, 8(SEP), 338. https://doi.org/10.3389/fnbeh.2014.00338

Schiepek, G., Tominschek, I., Heinzel, S., Aigner, M., Dold, M., Unger, A., Lenz, G., Windischberger, C., Moser, E., Plöderl, M., Lutz, J., Meindl, T., Zaudig, M., Pogarell, O., & Karch, S. (2013). Discontinuous Patterns of Brain Activation in the Psychotherapy Process of Obsessive-Compulsive Disorder: Converging Results from Repeated fMRI and Daily Self-Reports. PLoS ONE, 8(8), e71863. https://doi.org/10.1371/journal.pone.0071863

Schoenberg, P. L. A., & David, A. S. (2014). Biofeedback for Psychiatric Disorders: A Systematic Review. Applied Psychophysiology and Biofeedback, 39(2), 109–135. https://doi.org/10.1007/s10484-014-9246-9

Seibell, P., & Hollander, E. (2014). Management of Obsessive-Compulsive Disorder. F1000Prime Reports, 6(August), 1–6. https://doi.org/10.12703/P6-68

Shannahoff-khalsa, D. S., & Beckett, L. R. (1996). Clinical Case Report: Efficacy of Yogic Techniques in the Treatment of Obsessive Compulsive D Isorders. International Journal of Neuroscience, 85(1–2), 1–17. https://doi.org/10.3109/00207459608986347

Shannahoff-Khalsa, D. S., Ray, L. E., Levine, S., Gallen, C. C., Schwartz, B. J., & Sidorowich, J. J. (1999). Randomized Controlled Trial of Yogic Meditation Techniques for Patients With Obsessive-Compulsive Disorder. CNS Spectrums, 4(12), 34–47. https://doi.org/10.1017/S1092852900006805

Shen, X., Tokoglu, F., Papademetris, X., & Constable, R. T. (2013). Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. NeuroImage, 82(2), 403–415. https://doi.org/10.1016/j.neuroimage.2013.05.081

Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding Subject-Driven Cognitive States with Whole-Brain Connectivity Patterns. Cerebral Cortex, 22(1), 158–165. https://doi.org/10.1093/cercor/bhr099

Silva, D., & Campos, R. (1998). Alguns dados normativos do inventário de Estado-Traço de Ansiedade - Forma Y (STAI - Y), de Spielberger, para a população portuguesa. In Revista Portuguesa de Psicologia (Issue 33, pp. 71–89).

Simon, D., Kischkel, E., Spielberg, R., & Kathmann, N. (2012). A pilot study on the validity of using pictures and videos for individualized symptom provocation in obsessive–compulsive disorder. Psychiatry Research, 198(1), 81–88. https://doi.org/10.1016/j.psychres.2011.12.022

Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., Weiskopf, N., Blefari, M. L., Rana, M., Oblak, E., Birbaumer, N., & Sulzer, J. (2016). Closed-loop brain training: the science of neurofeedback. Nature Reviews Neuroscience, 18(2), 86–100. https://doi.org/10.1038/nrn.2016.164

Sokunbi, M. O., Linden, D. E. J., Habes, I., Johnston, S., & Ihssen, N. (2014). Real-time fMRI brain-computer interface: development of a â€œmotivational feedbackâ€ subsystem for the regulation of visual cue reactivity. Frontiers in Behavioral Neuroscience, 8(NOV). https://doi.org/10.3389/fnbeh.2014.00392

Sorger, B., Scharnowski, F., Linden, D. E. J., Hampson, M., & Young, K. D. (2019). Control freaks: Towards optimal selection of control conditions for fMRI neurofeedback studies. NeuroImage, 186(October 2018), 256–265. https://doi.org/10.1016/j.neuroimage.2018.11.004

Spielberger, C. D., Sydeman, S. J., Owen, A. E., & Marsh, B. J. (1999). Measuring anxiety and anger with the State-Trait Anxiety Inventory (STAI) and the State-Trait Anger Expression Inventory (STAXI). In The use of psychological testing for treatment planning and outcomes assessment. https://doi.org/http://dx.doi.org/10.1016/j.puhe.2011.01.004

Stein, D. J., Costa, D. L. C., Lochner, C., Miguel, E. C., Reddy, Y. C. J., Shavitt, R. G., van den Heuvel, O. A., & Simpson, H. B. (2019). Obsessive–compulsive disorder. Nature Reviews Disease Primers, 5(1), 52. https://doi.org/10.1038/s41572-019-0102-3

Stoeckel, L. E., Garrison, K. A., Ghosh, S. S., Wighton, P., Hanlon, C. A., Gilman, J. M., Greer, S., Turk-Browne, N. B., DeBettencourt, M. T., Scheinost, D., Craddock, C., Thompson, T., Calderon, V., Bauer, C. C., George, M., Breiter, H. C., Whitfield-Gabrieli, S., Gabrieli, J. D., LaConte, S. M., … Evins, A. E. (2014). Optimizing real time fMRI neurofeedback for therapeutic discovery and development. NeuroImage: Clinical, 5, 245–255. https://doi.org/10.1016/j.nicl.2014.07.002

Sürmeli, T., & Ertem, A. (2011). Obsessive Compulsive Disorder and the Efficacy of qEEG-Guided Neurofeedback Treatment: A Case Series. Clinical EEG and Neuroscience, 42(3), 195–201. https://doi.org/10.1177/155005941104200310

Thibault, R. T., MacPherson, A., Lifshitz, M., Roth, R. R., & Raz, A. (2018). Neurofeedback with fMRI: A critical systematic review. NeuroImage, 172(December 2017), 786–807. https://doi.org/10.1016/j.neuroimage.2017.12.071

Thorsen, A. L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., & van den Heuvel, O. A. (2018). Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-analysis of 25 Functional Neuroimaging Studies. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3(6), 563–571. https://doi.org/10.1016/J.BPSC.2018.01.009

Thorsen, A. L., van den Heuvel, O. A., Hansen, B., & Kvale, G. (2015). Neuroimaging of psychotherapy for obsessive–compulsive disorder: A systematic review. Psychiatry Research: Neuroimaging, 233(3), 306–313. https://doi.org/10.1016/j.pscychresns.2015.05.004

Tian, L., Meng, C., Jiang, Y., Tang, Q., Wang, S., Xie, X., Fu, X., Jin, C., Zhang, F., & Wang, J. (2016). Abnormal functional connectivity of brain network hubs associated with symptom severity in treatment-naive patients with obsessive–compulsive disorder: A resting-state functional MRI study. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 66, 104–111. https://doi.org/10.1016/j.pnpbp.2015.12.003

Tomas Ros, Stefanie Enriquez-Geppert, Vadim Zotev, Kymberly Young, Guilherme Wood, S., Whitfield-Gabrieli, Patrik Vuilleumier, Feng Wan, François Vialatte, Dimitri Van De Ville, D., Todder, Tanju Surmeli, James Sulzer, Ute Strehl, Barry Sterman, Naomi Steiner, Bettina Sorger, S., Soekadar, Ranganatha Sitaram, Leslie Sherlin, Michael Schönenberg, Frank Scharnowski, M., Schabus, Katya Rubia, Agostinho Rosa, Miriam Reiners, Jaime Pineda, Christian Paret, A., Ossadtchi, Andrew Nicholson, Wenya Nan, Javier Minguez, Jean-Arthur Micoulaud-Franchi, D., M. A. Mehler, Michael Lührs, Joel Lubar, Fabien Lotte, David E. J. Linden, J. L.-P., Mikhail Lebedev, Ruth Lanius, Andrea Kübler, Cornelia Kranczioch, Yury Koush, L. K., Simon H. Kohl, Silivia E. Kober, Manousos Klados, Camille Jeunet, Tieme Janssen, R. J. H., Kerstin Hoedlmoser, Laurence Hirshberg, Stephan Heunis, Talma Hendler, M. H., Adrian Guggisberg, John Gruzelier, Rainer Göbel, Nicolas Gninenko, Alireza Gharabaghi, P., Frewen, Thomas Fovet, Thalia Fernandez, Carlos Escolano, Ann-Christine Ehlis, R. D., R Christopher deCharms, Stefan Debener, Dirk

De Ridder, Eddy Davelaar, Marco Congedo, M., Cavazza, Rien M. H. M. Breteler, Daniel Brandeis, Jerzy Bodurka, Niels Birbaumer, O. B., & Robert Bauer, Beatrix Barth, Panagiotis Bamidis, Tibor Auer, Martijn Arns, R. T. T. (2019, October). Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist). PsyArXiv. https://doi.org/10.31234/osf.io/nyx84

Trevizol, A. P., Shiozawa, P., Cook, I. A., Sato, I. A., Kaku, C. B., Guimarães, F. B., Sachdev, P., Sarkhel, S., & Cordeiro, Q. (2016). Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder. The Journal of ECT, 32(4), 262–266. https://doi.org/10.1097/YCT.0000000000000335

Trigo, M., Canudo, N., Branco, F., & Silva, D. (2010). Estudo das propriedades psicométricas da Perceived Stress Scale (PSS) na população portuguesa. Psychologica, 10(53), 353–378. http://iduc.uc.pt/index.php/psychologica/article/view/1093

Tustison, N. J., Avants, B. B., Cook, P. A., Yuanjie Zheng, Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: Improved N3 Bias Correction. IEEE Transactions on Medical Imaging, 29(6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908

Vaz, F. M., Martins, C., & Martins, E. C. (2014). Diferenciação emocional e regulação emocional em adultos portugueses. PSICOLOGIA, 22(2), 123. https://doi.org/10.17575/rpsicol.v22i2.350

Veale, D., Miles, S., Smallcombe, N., Ghezai, H., Goldacre, B., & Hodsoll, J. (2014). Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis. BMC Psychiatry, 14(1), 317. https://doi.org/10.1186/s12888-014-0317-5

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. NeuroImage, 92, 381–397. https://doi.org/10.1016/j.neuroimage.2014.01.060

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal Autocorrelation in Univariate Linear Modeling of FMRI Data. NeuroImage, 14(6), 1370–1386. https://doi.org/10.1006/nimg.2001.0931

Xu, J., Moeller, S., Auerbach, E. J., Strupp, J., Smith, S. M., Feinberg, D. A., Yacoub, E., & Uğurbil, K. (2013). Evaluation of slice accelerations using multiband echo planar imaging at 3T. NeuroImage, 83(2), 991–1001. https://doi.org/10.1016/j.neuroimage.2013.07.055

Yang, X.-Y., Sun, J., Luo, J., Zhong, Z.-X., Li, P., Yao, S.-M., Xiong, H.-F., Huang, F.-F., & Li, Z.-J. (2015). Regional homogeneity of spontaneous brain activity in adult patients with obsessive–compulsive disorder before and after cognitive behavioural therapy. Journal of Affective Disorders, 188, 243–251. https://doi.org/10.1016/j.jad.2015.07.048

Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: Identifying differences in brain networks. NeuroImage, 53(4), 1197–1207. https://doi.org/10.1016/j.neuroimage.2010.06.041

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Transactions on Medical Imaging, 20(1), 45–57. https://doi.org/10.1109/42.906424

Zhao, H.-Z., Wang, C.-H., Gao, Z.-Z., Ma, J.-D., Huang, P., Li, H.-F., Sang, D.-E., Shan, X.-W., Kou, S.-J., Li, Z.-R., Ma, L., Zhang, Z.-H., Zhang, J.-H., Ouyang, H., Lian, H.-K., Zang, Y.-F., & Hu, X.-Z. (2017). Effectiveness of cognitive-coping therapy and alteration of resting-state brain function in obsessive-compulsive disorder. Journal of Affective Disorders, 208, 184–190. https://doi.org/10.1016/j.jad.2016.10.015

Zhou, D.-D., Zhou, X.-X., Li, Y., Zhang, K.-F., Lv, Z., Chen, X.-R., Wan, L.-Y., Wang, W., Wang, G.-M., Li, D.-Q., Ai, M., & Kuang, L. (2019). Augmentation agents to serotonin reuptake inhibitors for treatment-resistant obsessive-compulsive disorder: A network meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 90, 277–287. https://doi.org/10.1016/j.pnpbp.2018.12.009

Zotev, V., Phillips, R., Yuan, H., Misaki, M., & Bodurka, J. (2014). Self-regulation of human brain activity using simultaneous real-time fMRI and EEG neurofeedback. NeuroImage, 85, 985–995. https://doi.org/10.1016/j.neuroimage.2013.04.126

9. Supplementary material

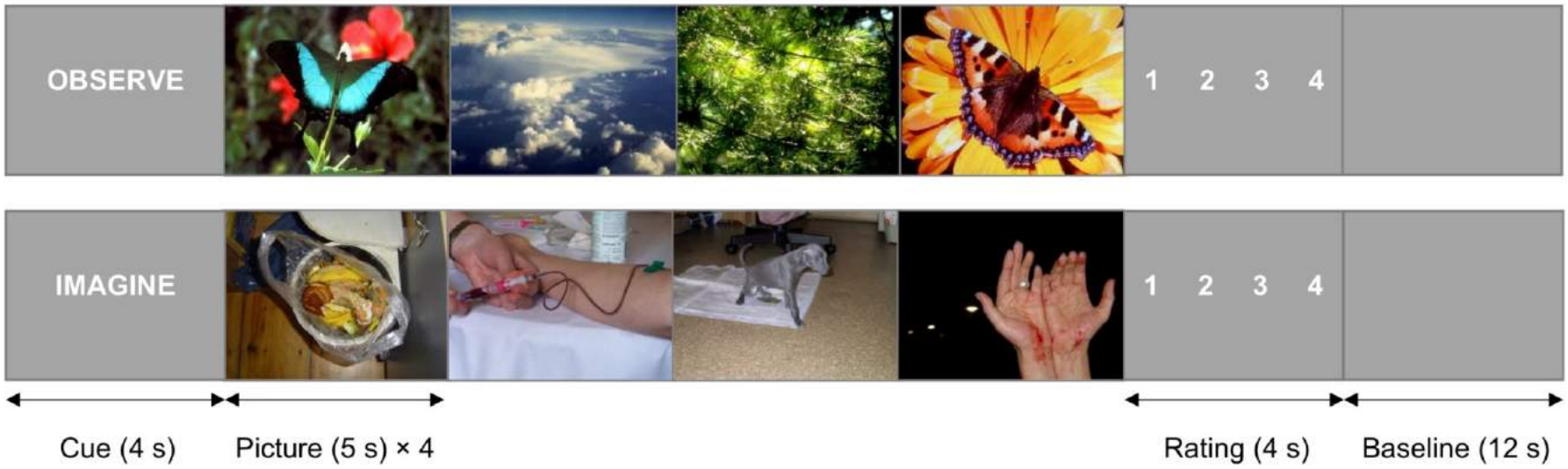


Figure S1 Representation of the localizer stimulus blocks with neutral or contamination-related pictures. Twelve neutral and 12 contamination blocks were randomly presented with 12 s baseline intervals. This stimulus was used to find the region of the orbitofrontal cortex for the neurofeedback sessions and to explore whole-brain functional differences induced by the neurofeedback training. The displayed neutral pictures were adapted from the International Affective Picture System (Lang et al., 1997, 2005) and the contamination-related images belong to the Berlin Obsessive Compulsive Disorder-Picture Set (Simon et al., 2012).

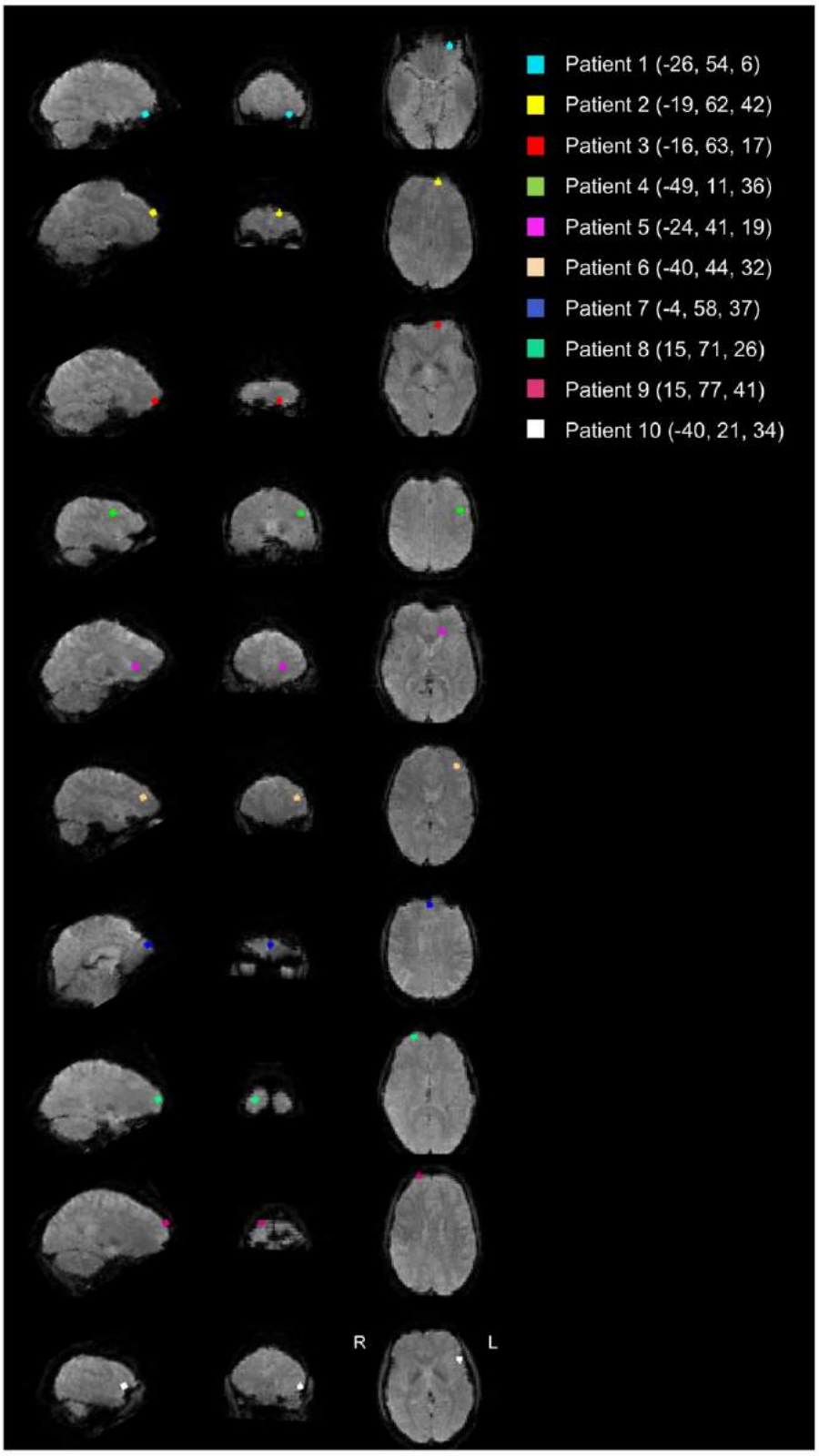


Figure S2 Representation of the regions targeted during neurofeedback for each patient in the native space. The coordinates are in mm. L – left, R – right.

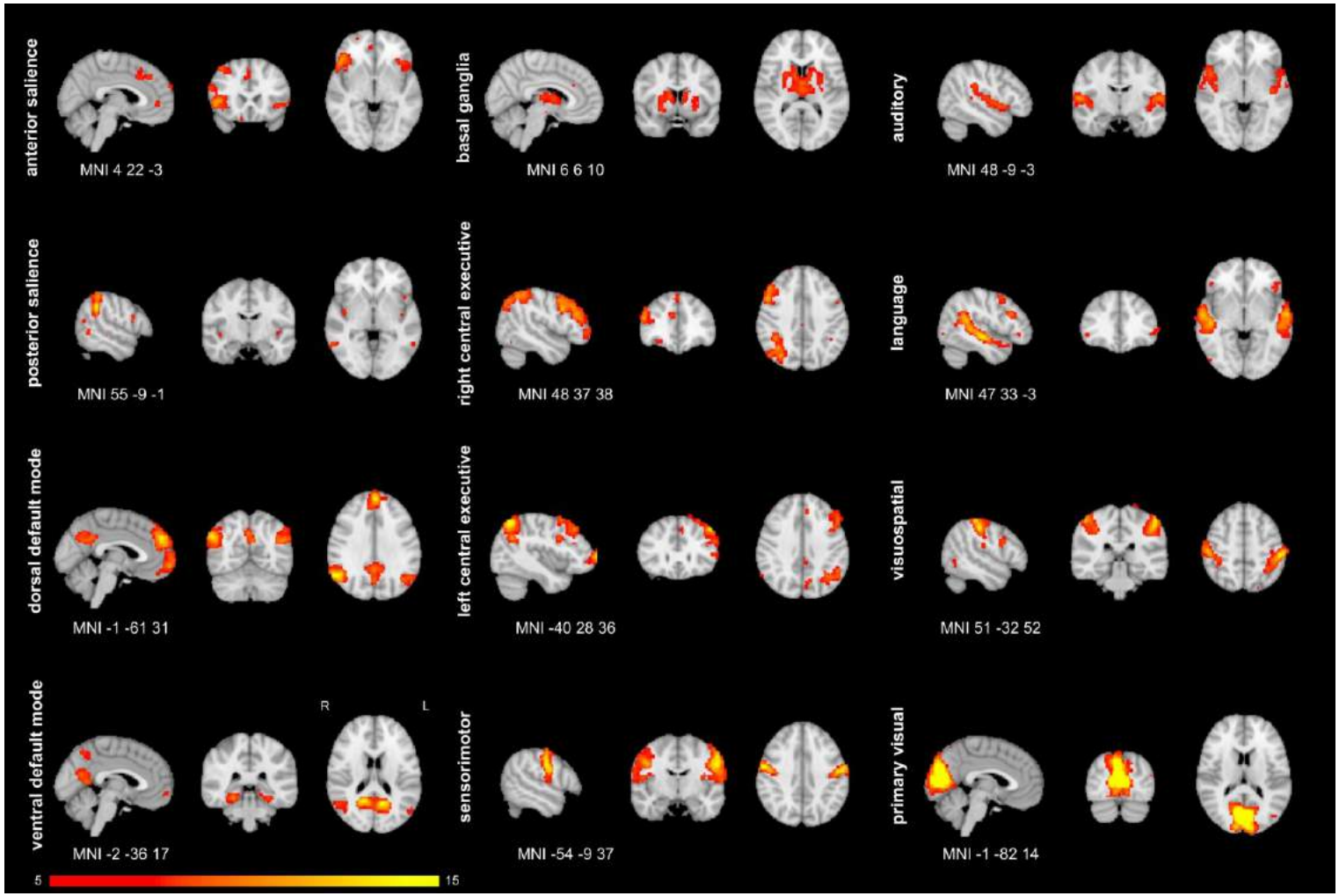


Figure S3 Resting-state networks identified after independent component analysis. The higher visual network and the precuneus network are not represented here but were also identified. R – right; L – left; MNI - Montreal Neurological Institute (coordinates in mm).

1. Discussion and future perspectives

Obsessive-compulsive disorder (OCD) impacts the processes of cognitive regulation of emotion and reward. The deficiencies in the self-regulation of obsessive thoughts cause highly distressful and anxious states (Derin & Yorulmaz, 2020; Hezel & McNally, 2016). Additionally, OCD patients seek for rewarding compulsive behaviors in response to the intrusive thoughts to obtain relief and safety-related sensations (Albertella et al., 2020; Barahona-Corrêa et al., 2015; Tarumi & Tashiro, 2004). However, the impairments in the neurobiological and behavioral mechanisms of cognitive regulation in OCD are still poorly described. This thesis provides further insights on this matter. Additionally, exposure to stress is associated with the onset of OCD and the aggravation of its symptomatology (Adams et al., 2018). Furthermore, stress also plays an important role in the cognitive regulation of emotion and reward (Cai et al., 2017; Goldfarb et al., 2020). In this way, we also explored the impact of stress levels on cognitive regulation of emotion and reward in terms of behavioral, neural, and psychometric measurements.

Chapter I provides a systematic review of the literature addressing cognitive regulation deficits in OCD with neurobiological, physiological, and behavioral variables. This review demonstrated that past studies focused on emotion regulation by using affective tasks, highlighting the absence of work in the field of cognitive regulation of reward (addressed in **Chapter IV**). Nevertheless, this review allowed the integration of information about behavioral and neural mechanisms associated with emotion regulation deficits. Agreeing with past literature, cognitive reappraisal and acceptance strategies are beneficial to reduce OCD symptoms (distress and frequency of obsessions) in contrast to suppression methods (X. Goldberg et al., 2016; Naragon-Gainey et al., 2017; Troy et al., 2018). The neuroimaging data revealed that OCD patients have mostly decreased brain function in dorsolateral prefrontal (dlPFC), posterior cingulate, superior temporal, and inferior parietal regions during emotion regulation with reappraisal and suppression strategies. This review also refers to the lack of studies using peripheral physiological measures of cognitive regulation in OCD. Heart rate and heart rate variability changes accordingly to emotional states are modulated by medial, orbitofrontal (OFC), and cingulate prefrontal regions (Thayer et al., 2009). Additionally, emotion regulation with reappraisal strategies translates into skin conductance (Troy et al., 2018) and electromyographic alterations (F. Li et al., 2018). These signals can be used as a surrogate of central nervous functioning to study emotion regulation. Thus, this field is an interesting area for future research exploring cognitive regulation deficits in OCD.

We also explored the efficacy of fMRI neurofeedback to tackle OCD symptoms. fMRI neurofeedback is based on the simultaneous integration of strategies for cognitive regulation and information about neural activity (Linhartová et al., 2019; Paret & Hendler, 2020). First, we conducted a meta-analysis on the efficacy of biofeedback approaches for obsessive-compulsive and related disorders, including neurofeedback studies (**Chapter V**). Our results revealed that past fMRI neurofeedback studies with OCD patients had small sample sizes and were not controlled. Moreover, we found a lack of studies with other biofeedback modalities (e.g. heart rate and skin conductance). Biofeedback has been successfully applied to several psychiatric disorders (Schoenberg & David, 2014). Thus, future studies with biofeedback techniques for emotion regulation might help OCD patients on a daily basis, for example in combination with digital and mobile technology (Ferreri et al., 2019). Given the scarcity of fMRI neurofeedback studies, we developed a protocol of fMRI neurofeedback for treatment-resistant patients (**Chapter VI**). We defined a double-blind and sham-controlled design. Although our findings are preliminary and require further comparison with the sham control group, we observed encouraging long-term reductions of obsessive-compulsive and stress symptoms after neurofeedback. However, only one-third of the patients responded after neurofeedback suggesting that prolonged protocols might be essential for better clinical outcomes. After neurofeedback, the response in a dlPFC/precentral region during symptomatic provocation augmented, and the negative connectivity at rest between OFC and temporoparietal regions increased.

Based on **Chapter I**, we can conclude that emotion regulation impairments in OCD are associated with decreased function in areas from the frontoparietal network (FPN) (Cocchi et al., 2013). These deficits may underly difficulties in switching attention away from intrusive thoughts and distress/anxiety states (de Vries et al., 2019; Gürsel et al., 2018) to reach the emotion regulation goal (Etkin et al., 2015; Gürsel et al., 2020). After neurofeedback treatment (**Chapter VI**), the dlPFC response seems to normalize possibly indicating a partial restoration of emotion regulation abilities (Paret & Hendler, 2020). Indeed, OCD patients learn how to use cognitive reappraisal strategies during the neurofeedback protocol. However, we did not observe changes in cognitive reappraisal and suppression scores after neurofeedback. Nonetheless, the obsessions score decreased at a trend level pointing to better control over intrusive thoughts. Additionally, the increase in the negative connectivity between OFC and temporoparietal regions may suggest decreased valuation and attention for negative emotions (Derin & Yorulmaz, 2020; Fontenelle et al., 2012). Furthermore, the OFC plays a role in inhibitory cognitive processes in connection with the dlPFC. Thus, neurofeedback may increase the functional connection between these regions leading to an improvement in cognitive regulation (H. J. Han et al., 2016).

In **Chapter II** we concluded that perceived stress levels modulate the impact of OCD on cognitive emotion regulation. Thus, the impairments in cognitive reappraisal are explained by a combination of obsessive-compulsive and stress symptoms. These results align with the hypothesis that stress contributes to the aggravation of OCD symptomology (Adams et al., 2018) and affects the cognitive regulation of emotions (Cai et al., 2017; Shermohammed et al., 2017). Nonetheless, future studies should address the neural mechanisms associated with the impact of stress on cognitive regulation of emotions in OCD. Stress might reinforce the functional deficits in dlPFC regions during emotion regulation (as described in **Chapter I**) leading to an exacerbation of the distress elicited by intrusive thoughts (Arnsten, 2009; McEwen & Morrison, 2013; N. Sousa, 2016). Studies combining stress management and cognitive-behavioral therapy might also bring new insights into this matter (Cruess et al., 2015; Schumer et al., 2018). Indeed, we observed decreased perceived stress and obsessive-compulsive scores three months after neurofeedback, although no emotion regulation changes were found (**Chapter VI**). These findings strengthen the idea of an interplay between stress and OCD. Importantly, other factors besides stress may play a role in emotion regulation deficits in OCD patients such as personality traits (Barańczuk, 2019; Hughes et al., 2020). For example, OCD individuals have high scores on neuroticism that make them more vulnerable to stress and anxiety and more prone to the use suppression and avoidance strategies (Barańczuk, 2019; X. Goldberg et al., 2016; Hughes et al., 2020; Tang et al., 2018). Thus, future studies should account for more complex models to analyze the influence of other factors.

Lastly, in **Chapters III** and **IV** we focused on the cognitive regulation of reward. In terms of behavior, we found that chronic stress reduces the valuation of food rewards, but the neuroimaging results did not show changes in brain activation during cognitive regulation and reward valuation. However, we did not explore functional connectivity alterations during the performance of the task. Indeed, previous studies point to impairments of dlPFC function and cognitive flexibility and attentional shifting after acute and chronic stress (Arnsten, 2009; McEwen & Morrison, 2013). For the OCD sample, we observed inflexible behavior during reward valuation after the cognitive regulation of craving. Moreover, we found FPN hyperconnectivity during cognitive regulation and augmented connectivity between ventromedial prefrontal (vmPFC) and posterior cingulate and temporoparietal areas while the patients were valuating food rewards. Thus, chronic stress seems to reduce the value attributed to rewards (Herzberg & Gunnar, 2020) while obsessive-compulsive symptoms may impact goal-direct behavior during reward valuation (Caudek et al., 2020). The increased connectivity between vmPFC and cingulate areas might be related to amplified habitual behavior during the valuation of rewards (Etkin et al., 2015; Koch et al., 2018). Temporoparietal, cingulate, and dlPFC regions are involved in the self-regulation of food rewards (J. E.

Han et al., 2018). Indeed, the increased connectivity between dlPFC and inferior parietal regions during cognitive regulation suggests an increased effort for attentional shifting and goal maintenance due to excessive monitoring of intrusive thoughts (Barahona-Corrêa et al., 2015; Göttlich et al., 2014; Gürsel et al., 2020; Stern et al., 2017) in OCD patients. These results agree with the emotion regulation deficits found in OCD patients (**Chapter I**) associated with hypoactivity in dlPFC and inferior parietal regions. In this way, the impairment of neural pathways underlying cognitive regulation of emotion and reward may overlap in OCD. Recent meta-analysis studies suggest that the dlPFC and inferior parietal cortex are similarly activated during regulation of reward and emotion in line with our conclusions (Brandl et al., 2019; J. E. Han et al., 2018). Additionally, both reward and emotion processing involve the perception, valuation and action/response for salient stimuli and the goal-directed decision to cognitive regulate or not this response based on the costs and benefits of the regulation (Etkin et al., 2015; J. E. Han et al., 2018; Langner et al., 2018). Other authors also found that emotion suppression is linked to blunted reward responsivity (Kelley et al., 2019). Nonetheless, future studies should further explore the mechanisms of cognitive regulation of reward in OCD and the impact of stress on these processes.

Figure 1 represents an overview of the main findings of this thesis.

2. Limitations

The major limitation of the work developed in this thesis is the inclusion of small samples. Importantly, neuroimaging analyses are affected by the variability inherent to small samples (X. Chen et al., 2018; Cremers et al., 2017). Nonetheless, our results follow the direction of past research concerning cognitive regulation impairments in OCD. Moreover, we provided novel insights about the mechanisms underlying reward regulation deficits and neurofeedback effects in OCD, and regarding the effects of stress in this disorder. Future replication studies with larger samples can provide additional robustness to our findings. Additionally, a larger sample size allows the disentangling of cognitive regulation impairments specific for different OCD dimensions (García-Soriano & Belloch, 2013).

The inclusion of patients under pharmacological treatment is an additional constraint to the validity of our conclusions. Antidepressant medication affects the function and connectivity of brain circuits and the behavior associated with emotion regulation (Carthy et al., 2017; Outhred et al., 2013; Wagner et al., 2017). Moreover, the psychotherapy-based treatment causes alterations in neural functioning and improves cognitive regulation abilities (Baioui et al., 2013; Brooks & Stein, 2015). Thus, the deficits

observed in treatment-naïve patients might be mitigated after treatment. In this way, forthcoming studies must focus on naïve patients. Additionally, the comparison of OCD patients with unaffected siblings can provide information on OCD endophenotypes related to cognitive regulation (de Vries et al., 2019; A. L. L. Thorsen et al., 2019).

Herein, we used a craving regulation task as a proxy of reward regulation in OCD which may pose limitations to the generalization of results to the disorder context. Thus, the development of more ecological paradigms to analyze cognitive regulation mechanisms in OCD might be advantageous (Abramovitch, McCormack, et al., 2019), for example, the study of the spontaneous use of regulation strategies to cope with naturally occurring intrusive thoughts, anxiety/distress states, and compulsions (Aldao et al., 2013; Volokhov & Demaree, 2010).

3. Conclusions

Deficits in cognitive regulation may arise from OCD's excessive belief of the importance of controlling thoughts. Thus, OCD patients are excessively focused on internal states consequently lacking the cognitive flexibility to switch their attentional resources and to direct their goal-related abilities away from intrusive thoughts and distress states to regulate emotion and reward. The cognitive regulation deficits are associated with alterations in the FPN functioning. Additionally, the impact of stress on dlPFC responses may lead to an exacerbation of cognitive regulation impairments.

Our findings suggest that the inclusion of stress management in psychotherapy approaches might be beneficial to improve cognitive regulation skills in OCD patients. Moreover, neurostimulation or neurofeedback protocols targeting FPN regions could be advantageous for cognitive regulation abilities.

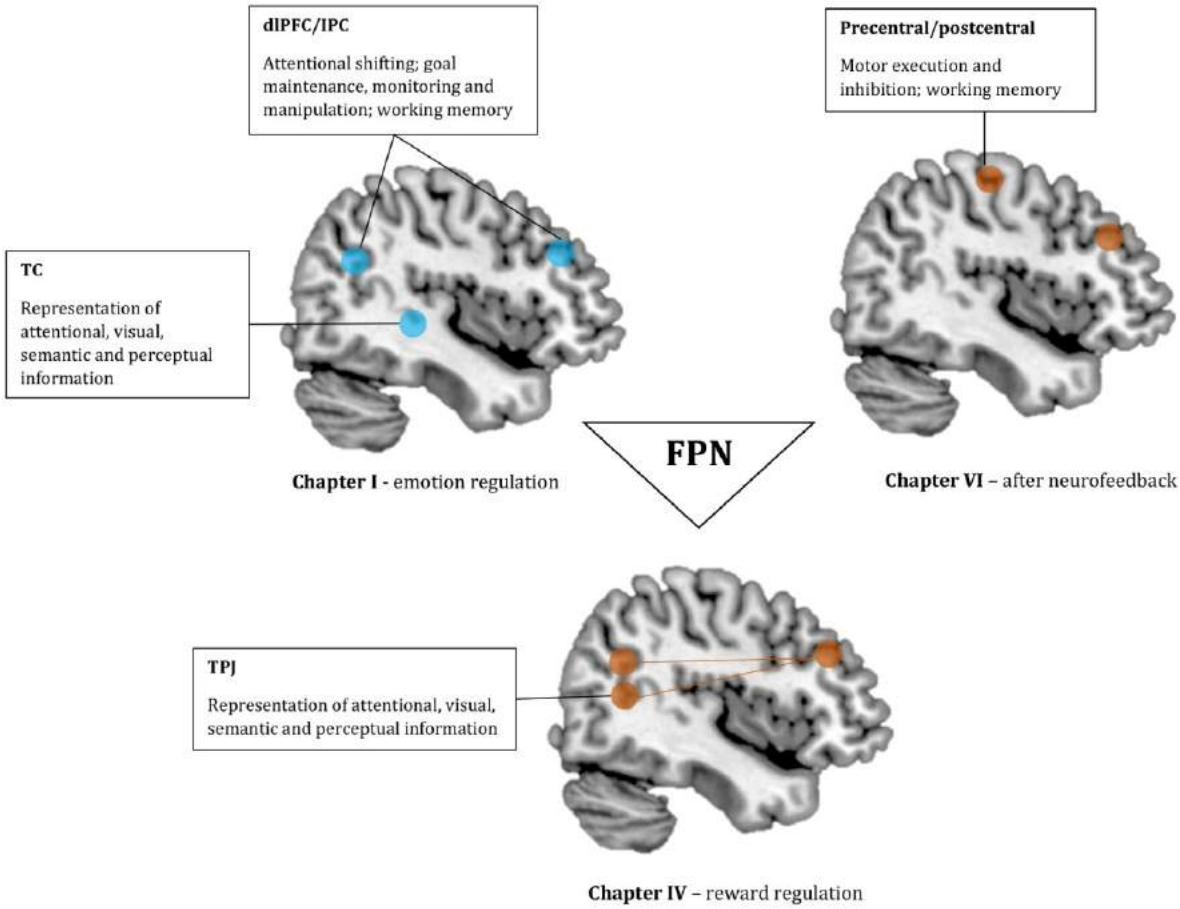


Figure 1 Representation of the main findings of the thesis. Regions belonging to the frontoparietal network (FPN) display decreased (blue color) activity during cognitive regulation of emotion, increased (orange color) responses after neurofeedback, and augmented functional connectivity during cognitive regulation of reward. The figure was created with MRIcron templates (https://people.cas.sc.edu/rorden/mricron/). The regions were drawn for illustrative purposes and do not represent the exact anatomical location. dlPFC – dorsolateral prefrontal cortex; IPC – inferior parietal cortex; TPJ – temporoparietal junction; TC – temporal cortex.

4. References

Abramovitch, A., McCormack, B., Brunner, D., Johnson, M., & Wofford, N. (2019). The impact of symptom severity on cognitive function in obsessive-compulsive disorder: A meta-analysis. Clinical Psychology Review, 67, 36–44. https://doi.org/10.1016/j.cpr.2018.09.003

Adams, T. G., Kelmendi, B., Brake, C. A., Gruner, P., Badour, C. L., & Pittenger, C. (2018). The Role of Stress in the Pathogenesis and Maintenance of Obsessive-Compulsive Disorder. Chronic Stress, 2(1), 247054701875804. https://doi.org/10.1177/2470547018758043

Albertella, L., Le Pelley, M. E., Chamberlain, S. R., Westbrook, F., Lee, R. S. C., Fontenelle, L. F., Grant, J. E., Segrave, R., McTavish, E., & Yücel, M. (2020). Reward-related attentional capture and cognitive inflexibility interact to determine greater severity of compulsivity-related problems. Journal of Behavior Therapy and Experimental Psychiatry, 101580. https://doi.org/10.1016/j.jbtep.2020.101580

Aldao, A., Mennin, D. S., & McLaughlin, K. A. (2013). Differentiating Worry and Rumination: Evidence from Heart Rate Variability During Spontaneous Regulation. Cognitive Therapy and Research, 37(3), 613–619. https://doi.org/10.1007/s10608-012-9485-0

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. Nature Reviews Neuroscience, 10(6), 410–422. https://doi.org/10.1038/nrn2648

Baioui, A., Pilgramm, J., Kagerer, S., Walter, B., Vaitl, D., & Stark, R. (2013). Neural correlates of symptom reduction after CBT in obsessive-compulsive washers—An fMRI symptom provocation study. Journal of Obsessive-Compulsive and Related Disorders, 2(3), 322–330. https://doi.org/10.1016/j.jocrd.2013.04.006

Barahona-Corrêa, J. B., Camacho, M., Castro-Rodrigues, P., Costa, R., & Oliveira-Maia, A. J. (2015). From Thought to Action: How the Interplay Between Neuroscience and Phenomenology Changed Our Understanding of Obsessive-Compulsive Disorder. Frontiers in Psychology, 6(NOV). https://doi.org/10.3389/fpsyg.2015.01798

Barańczuk, U. (2019). The five factor model of personality and emotion regulation: A meta-analysis. Personality and Individual Differences, 139(July 2018), 217–227. https://doi.org/10.1016/j.paid.2018.11.025

Brandl, F., Le Houcq Corbi, Z., Mulej Bratec, S., & Sorg, C. (2019). Cognitive reward control recruits medial and lateral frontal cortices, which are also involved in cognitive emotion regulation: A coordinate-based meta-analysis of fMRI studies. NeuroImage, 200(August 2018), 659–673. https://doi.org/10.1016/j.neuroimage.2019.07.008

Brooks, S. J., & Stein, D. J. (2015). A systematic review of the neural bases of psychotherapy for anxiety and related disorders. Dialogues in Clinical Neuroscience, 17(3), 261–279. http://www.ncbi.nlm.nih.gov/pubmed/26487807

Cai, W., Pan, Y., Zhang, S., Wei, C., Dong, W., & Deng, G. (2017). Relationship between cognitive emotion regulation, social support, resilience and acute stress responses in Chinese soldiers: Exploring multiple mediation model. Psychiatry Research, 256, 71–78. https://doi.org/10.1016/j.psychres.2017.06.018

Carthy, T., Benaroya-Milshtein, N., Valevski, A., & Apter, A. (2017). Emotional Reactivity and Regulation Following Citalopram Therapy in Children and Adolescents with Anxiety Disorders. Journal of Child and Adolescent Psychopharmacology, 27(1), 43–51. https://doi.org/10.1089/cap.2015.0067

Caudek, C., Sica, C., Marchetti, I., Colpizzi, I., & Stendardi, D. (2020). Cognitive inflexibility specificity for individuals with high levels of obsessive-compulsive symptoms. Journal of Behavioral and Cognitive Therapy, 30(2), 103–113. https://doi.org/10.1016/j.jbct.2020.03.010

Chen, X., Lu, B., & Yan, C.-G. (2018). Reproducibility of R-fMRI metrics on the impact of different strategies for multiple comparison correction and sample sizes. Human Brain Mapping, 39(1), 300–318. https://doi.org/10.1002/hbm.23843

Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. Trends in Cognitive Sciences, 17(10), 493–501. https://doi.org/10.1016/j.tics.2013.08.006

Cremers, H. R., Wager, T. D., & Yarkoni, T. (2017). The relation between statistical power and inference in fMRI. PLOS ONE, 12(11), e0184923. https://doi.org/10.1371/journal.pone.0184923

Cruess, D. G., Finitsis, D. J., Smith, A.-L., Goshe, B. M., Burnham, K., Burbridge, C., & O'Leary, K. (2015). Brief stress management reduces acute distress and buffers physiological response to a social stress test. International Journal of Stress Management, 22(3), 270–286. https://doi.org/10.1037/a0039130

de Vries, F. E., de Wit, S. J., van den Heuvel, O. A., Veltman, D. J., Cath, D. C., van Balkom, A. J. L. M., & van der Werf, Y. D. (2019). Cognitive control networks in OCD: A resting-state connectivity study in unmedicated patients with obsessive-compulsive disorder and their unaffected relatives. The World Journal of Biological Psychiatry, 20(3), 230–242. https://doi.org/10.1080/15622975.2017.1353132

Derin, S., & Yorulmaz, O. (2020). Cognitive Bias Modification in Obsessive Compulsive Disorder. Psikiyatride Guncel Yaklasimlar - Current Approaches in Psychiatry, 12(3), 299–317. https://doi.org/10.18863/pgy.620707

Etkin, A., Büchel, C., & Gross, J. J. (2015). The neural bases of emotion regulation. Nature Reviews Neuroscience, 16(11), 693–700. https://doi.org/10.1038/nrn4044

Ferreri, F., Bourla, A., Peretti, C.-S., Segawa, T., Jaafari, N., & Mouchabac, S. (2019). How New Technologies Can Improve Prediction, Assessment, and Intervention in Obsessive-Compulsive Disorder (e-OCD): Review. JMIR Mental Health, 6(12), e11643. https://doi.org/10.2196/11643

Fontenelle, L., Harrison, B., Pujol, J., Davey, C., Fornito, A., Bora, E., Pantelis, C., & Yücel, M. (2012). Brain functional connectivity during induced sadness in patients with obsessive–compulsive disorder. Journal of Psychiatry & Neuroscience, 37(4), 231–240. https://doi.org/10.1503/jpn.110074

García-Soriano, G., & Belloch, A. (2013). Symptom dimensions in obsessive-compulsive disorder: Differences in distress, interference, appraisals and neutralizing strategies. Journal of Behavior Therapy and Experimental Psychiatry, 44(4), 441–448. https://doi.org/10.1016/j.jbtep.2013.05.005

Goldberg, X., Cardoner, N., Alonso, P., López-Solà, C., Real, E., Hernández-Ribas, R., Jiménez-Murcia, S., Subirà, M., Segalàs, C., Menchón, J. M., & Soriano-Mas, C. (2016). Inter-individual variability in emotion regulation: Pathways to obsessive-compulsive symptoms. Journal of Obsessive-Compulsive and Related Disorders, 11, 105–112. https://doi.org/10.1016/j.jocrd.2016.10.002

Goldfarb, E. V., Rosenberg, M. D., Seo, D., Constable, R. T., & Sinha, R. (2020). Hippocampal seed connectome-based modeling predicts the feeling of stress. Nature Communications, 11(1), 2650. https://doi.org/10.1038/s41467-020-16492-2

Göttlich, M., Krämer, U. M., Kordon, A., Hohagen, F., & Zurowski, B. (2014). Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. Human Brain Mapping, 35(11), 5617–5632. https://doi.org/10.1002/hbm.22574

Gürsel, D. A., Avram, M., Sorg, C., Brandl, F., & Koch, K. (2018). Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. Neuroscience & Biobehavioral Reviews, 87(October 2017), 151–160. https://doi.org/10.1016/j.neubiorev.2018.01.016

Gürsel, D. A., Reinholz, L., Bremer, B., Schmitz-Koep, B., Franzmeier, N., Avram, M., & Koch, K. (2020). Frontoparietal and salience network alterations in obsessive–compulsive disorder: insights from

independent component and sliding time window analyses. Journal of Psychiatry and Neuroscience, 45(3), 214–221. https://doi.org/10.1503/jpn.190038

Han, H. J., Jung, W. H., Yun, J.-Y., Park, J. W., Cho, K. K., Hur, J.-W., Shin, N. Y., Lee, T. Y., & Kwon, J. S. (2016). Disruption of effective connectivity from the dorsolateral prefrontal cortex to the orbitofrontal cortex by negative emotional distraction in obsessive–compulsive disorder. Psychological Medicine, 46(5), 921–932. https://doi.org/10.1017/S0033291715002391

Han, J. E., Boachie, N., Garcia-Garcia, I., Michaud, A., & Dagher, A. (2018). Neural correlates of dietary self-control in healthy adults: A meta-analysis of functional brain imaging studies. Physiology and Behavior, 192, 98–108. https://doi.org/10.1016/j.physbeh.2018.02.037

Herzberg, M. P., & Gunnar, M. R. (2020). Early life stress and brain function: Activity and connectivity associated with processing emotion and reward. NeuroImage, 209(June 2019), 116493. https://doi.org/10.1016/j.neuroimage.2019.116493

Hezel, D. M., & McNally, R. J. (2016). A Theoretical review of cognitive biases and deficits in obsessive–compulsive disorder. Biological Psychology, 121, 221–232. https://doi.org/10.1016/j.biopsycho.2015.10.012

Hughes, D. J., Kratsiotis, I. K., Niven, K., & Holman, D. (2020). Personality traits and emotion regulation: A targeted review and recommendations. Emotion, 20(1), 63–67. https://doi.org/10.1037/emo0000644

Kelley, N. J., Glazer, J. E., Pornpattananangkul, N., & Nusslock, R. (2019). Reappraisal and suppression emotion-regulation tendencies differentially predict reward-responsivity and psychological well-being. Biological Psychology, 140, 35–47. https://doi.org/10.1016/j.biopsycho.2018.11.005

Koch, K., Reeß, T. J., Rus, O. G., Gürsel, D. A., Wagner, G., Berberich, G., & Zimmer, C. (2018). Increased Default Mode Network Connectivity in Obsessive–Compulsive Disorder During Reward Processing. Frontiers in Psychiatry, 9(JUN), 1–9. https://doi.org/10.3389/fpsyt.2018.00254

Langner, R., Leiberg, S., Hoffstaedter, F., & Eickhoff, S. B. (2018). Towards a human self-regulation system: Common and distinct neural signatures of emotional and behavioural control. Neuroscience & Biobehavioral Reviews, 90(1), 400–410. https://doi.org/10.1016/j.neubiorev.2018.04.022

Li, F., Yin, S., Feng, P., Hu, N., Ding, C., & Chen, A. (2018). The cognitive up- and down-regulation of positive emotion: Evidence from behavior, electrophysiology, and neuroimaging. Biological Psychology, 136(July 2017), 57–66. https://doi.org/10.1016/j.biopsycho.2018.05.013

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. NeuroImage, 193(March), 75–92. https://doi.org/10.1016/j.neuroimage.2019.03.011

McEwen, B. S., & Morrison, J. H. (2013). The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. Neuron, 79(1), 16–29. https://doi.org/10.1016/j.neuron.2013.06.028

Naragon-Gainey, K., McMahon, T. P., & Chacko, T. P. (2017). The structure of common emotion regulation strategies: A meta-analytic examination. Psychological Bulletin, 143(4), 384–427. https://doi.org/10.1037/bul0000093

Outhred, T., Hawkshead, B. E., Wager, T. D., Das, P., Malhi, G. S., & Kemp, A. H. (2013). Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: Implications for differential treatment efficacy. Neuroscience & Biobehavioral Reviews, 37(8), 1786–1800. https://doi.org/10.1016/j.neubiorev.2013.07.010

Paret, C., & Hendler, T. (2020). Live from the “regulating brain”: Harnessing the brain to change emotion. Emotion, 20(1), 126–131. https://doi.org/10.1037/emo0000674

Schoenberg, P. L. A., & David, A. S. (2014). Biofeedback for Psychiatric Disorders: A Systematic Review. Applied Psychophysiology and Biofeedback, 39(2), 109–135. https://doi.org/10.1007/s10484-014-9246-9

Schumer, M. C., Lindsay, E. K., & Creswell, J. D. (2018). Brief mindfulness training for negative affectivity: A systematic review and meta-analysis. Journal of Consulting and Clinical Psychology, 86(7), 569–583. https://doi.org/10.1037/ccp0000324

Shermohammed, M., Mehta, P. H., Zhang, J., Brandes, C. M., Chang, L. J., & Somerville, L. H. (2017). Does Psychosocial Stress Impact Cognitive Reappraisal? Behavioral and Neural Evidence. Journal of Cognitive Neuroscience, 29(11), 1803–1816. https://doi.org/10.1162/jocn_a_01157

Sousa, N. (2016). The dynamics of the stress neuromatrix. Molecular Psychiatry, 21(3), 302–312. https://doi.org/10.1038/mp.2015.196

Stern, E. R., Muratore, A. F., Taylor, S. F., Abelson, J. L., Hof, P. R., & Goodman, W. K. (2017). Switching between internally and externally focused attention in obsessive-compulsive disorder: Abnormal visual cortex activation and connectivity. Psychiatry Research: Neuroimaging, 265(August 2016), 87–97. https://doi.org/10.1016/j.pscychresns.2016.08.006

Tang, H.-S., Chen, P.-F., & Lung, F.-W. (2018). Personality and Alexithymic Disparity in Obsessive-Compulsive Disorder Based on Washing and Checking. Psychiatric Quarterly, 89(2), 371–381. https://doi.org/10.1007/s11126-017-9541-8

Tarumi, S., & Tashiro, N. (2004). Stress Situations of Daily Living in Patients with Obsessive—Compulsive Disorder: A Retrospective Case Note Study. Psychological Reports, 94(1), 139–150. https://doi.org/10.2466/pr0.94.1.139-150

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. Annals of Behavioral Medicine, 37(2), 141–153. https://doi.org/10.1007/s12160-009-9101-z

Thorsen, A. L. L., de Wit, S. J. J., de Vries, F. E. E., Cath, D. C. C., Veltman, D. J. J., van der Werf, Y. D. D., Mataix-Cols, D., Hansen, B., Kvale, G., & van den Heuvel, O. A. A. (2019). Emotion Regulation in Obsessive-Compulsive Disorder, Unaffected Siblings, and Unrelated Healthy Control Participants. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4(4), 352–360. https://doi.org/10.1016/j.bpsc.2018.03.007

Troy, A. S., Shallcross, A. J., Brunner, A., Friedman, R., & Jones, M. C. (2018). Cognitive reappraisal and acceptance: Effects on emotion, physiology, and perceived cognitive costs. Emotion, 18(1), 58–74. https://doi.org/10.1037/emo0000371

Volokhov, R. N., & Demaree, H. A. (2010). Spontaneous emotion regulation to positive and negative stimuli. Brain and Cognition, 73(1), 1–6. https://doi.org/10.1016/j.bandc.2009.10.015

Wagner, G., de la Cruz, F., Köhler, S., & Bär, K.-J. (2017). Treatment Associated Changes of Functional Connectivity of Midbrain/Brainstem Nuclei in Major Depressive Disorder. Scientific Reports, 7(1), 8675. https://doi.org/10.1038/s41598-017-09077-5

APPENDIX A

Ethics committee approval - University of Minho

Universidade do Minho

SECVS

Subcomissão de Ética para as Ciências da Vida e da Saúde

Identificação do documento: SECVS – 035/2013

Título do projeto: Regulação cognitiva durante a tomada de decisão em estudantes de medicina

Investigador(a) responsável: Dr. Pedro Morgado, da Escola de Ciências da Saúde (ECS) e do Hospital de Braga, Dr. Nuno Sousa, da Escola de Ciências da Saúde (ECS) e do Hospital de Braga, e Carlos Daniel Fernandes Veiga, aluno do Mestrado Integrado em Medicina da ECS-UMinho

Subunidade orgânica: Escola Ciências da Saúde, Universidade do Minho

Outras Unidades: Centro Clínico Académico-Braga

PARECER

A Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS) analisou o processo relativo ao projeto de investigação intitulado "*Regulação cognitiva durante a tomada de decisão em estudantes de medicina*".
Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na experimentação com humanos, em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde.
Face ao exposto, a SECVS nada tem a opor à realização do projeto.

Braga, 16 de julho de 2013.

A Presidente

(Maria Cecília de Lemos Pinto Estrela Leão)

Universidade do Minho

SECVS

Subcomissão de Ética para as Ciências da Vida e da Saúde

Identificação do documento: SECVS 154/2017

Título do projeto: *Autorregulação da ansiedade em doentes obsessivo-compulsivos - Do laboratório para uma aplicação da vida real ("Self-regulation of anxiety in obsessive-compulsive patients – from the lab to a real-life application")*

Investigador(a) responsável: Pedro Morgado, da Escola de Medicina (EM), do Instituto de Investigação em Ciências da Vida e da Saúde (ICVS) e do ICVS/3B's - Laboratório Associado, e do Hospital de Braga; José Miguel Gomes Moreira Pêgo, da Escola de Medicina (EM), do Instituto de Investigação em Ciências da Vida e da Saúde (ICVS) e do ICVS/3B's - Laboratório Associado; e a aluna de doutoramento Sónia Maria Gomes de Amaral Ferreira, da Escola de Medicina da Universidade do Minho

Subunidade orgânica: Escola de Medicina, Universidade do Minho

Outras Unidades: Serviço de Psiquiatria, Hospital de Braga; Centro Clinico Académico-Braga (2CA-Braga)

PARECER

A Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS) analisou o processo relativo ao projeto intitulado *Autorregulação da ansiedade em doentes obsessivo-compulsivos - Do laboratório para uma aplicação da vida real ("Self-regulation of anxiety in obsessive-compulsive patients – from the lab to a real-life application").*

Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na experimentação com humanos, em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde.

Face ao exposto, a SECVS nada tem a opor à realização do projeto.

Braga, 17 de janeiro de 2018.

A Presidente

MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO

Assinado de forma digital por MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
Dados: 2018.01.18 09:40:43 Z

Maria Cecília de Lemos Pinto Estrela Leão

Universidade do Minho

Conselho de Ética

Comissão de Ética para a Investigação em Ciências da Vida e da Saúde (CEICVS)

Identificação do documento: CEICVS 057/2019

Título do projeto: Alteração nos mecanismos neurobiológicos associados às tomadas de decisão em indivíduos com Perturbação Obsessivo-Compulsiva.

Equipa de Investigação: Maria Beatriz Azevedo Couto (A75548) (Investigadora Responsável), aluna do 6° ano do Mestrado Integrado em Medicina da Escola de Medicina (UM); Pedro Morgado (MD, PhD) (Orientador), Escola de Medicina da Universidade do Minho, Serviço de Psiquiatria-Hospital de Braga, Centro Clínico Académico – Braga; Ana Matilde Gomes, estudante do Mestrado Integrado em Medicina na Escola de Medicina da Universidade do Minho; Maria Picó Pérez (PhD), estudante de Licenciatura em Ciências da Computação da Universidade Aberta da Catalunha, Barcelona; Sónia Ferreira (MSc), estudante do Programa de Doutoramento em Ciências da Saúde Aplicadas, da Escola de Medicina da Universidade do Minho

Unidade Orgânica Promotora: Escola de Medicina da Universidade do Minho e Centro Clínico Académico-Braga.

Outras Unidades: Serviço de Psiquiatria do Hospital de Braga

PARECER

De acordo com a documentação apresentada, o projeto insere-se no âmbito da Unidade Curricular Projeto de Opção (PO) - Estágio Final do Mestrado Integrado em Medicina da Universidade do Minho e no âmbito da investigação desenvolvida no Centro Clínico Académico do Hospital de Braga. É um projeto financiado por verbas do orçamento do Instituto de Investigação em Ciências da Vida e Saúde da Universidade do Minho – Escola de Medicina da Universidade do Minho (fundos institucionais), não implicando custos para o Hospital de Braga.

Trata-se de um estudo prospetivo caso-controlo emparelhado, observacional, transversal, descritivo e analítico, que tem como objetivos principais: Caracterizar as tomadas de decisão nos doentes com Perturbação Obsessivo-Compulsiva; Compreender, do ponto de vista neuroanatómico e neurofuncional, os padrões de ativação cerebral durante tarefas de tomada de decisão nos doentes com Perturbação Obsessivo-Compulsiva; Comparar as tomadas de decisão e os padrões de ativação cerebral durante esta tarefa nos doentes com Perturbação Obsessivo Compulsiva com os controlos.

Após verificação e análise dos documentos associados ao processo de pedido de emissão de parecer ético sobre o projeto em apreço, a que reporta sumariamente a respetiva "Grelha de verificação e avaliação ética", considera-se que (i) o processo está devidamente instruído, (ii) a análise dos documentos apresentados sobre o estudo a realizar obedecem às regras de conduta ética e requisitos exigidos para as boas práticas na experimentação com humanos e (iii) estão em conformidade com o Guião para submissão de processos a pedido de Parecer Ético na UMinho.

Face ao exposto, a Comissão de Ética para a Investigação em Ciências da Vida e da Saúde (CEICVS) nada tem a opor à realização do projeto, emitindo o seu parecer favorável, que foi aprovado pelos seus membros.

Braga, 31 de outubro de 2019

A Presidente da CEICVS

MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO

Assinado de forma digital por MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
Dados: 2019.11.04 17:52:58 Z

.....

ANÁLISE E JUSTIFICAÇÃO DO PARECER

Relatora: Inês Sousa

Grelha de verificação e de avaliação ética

(Processo submetido em suporte eletrónico - documentos recebidos assinalados com X e respetiva avaliação ética)

Documentos	Sim	Não	Não se aplica	Avaliação Técnico-ética
Pedido de apreciação de projeto enviado à CEICVS *	X			Adequado

Quando aplicável, identificação da Unidade Curricular (UC) no âmbito da qual se insere o projeto (designação do curso, designação da UC e respetivo ano curricular, identificação do/s coordenador/es da UC, identificação do estudante)	X			Projeto de Opção (PO) - Estágio Final do Mestrado Integrado em Medicina da Escola de Medicina da Universidade do Minho (6º ano) da aluna Maria Beatriz Azevedo Couto (A75548)
Carta de Apoio/Autorização da(s) Unidade(s) ou Serviço(s) onde decorrerá o projeto [a]	X			Adequada
Quando aplicável, informação do Orientador da Tese sobre apoio e/ou enquadramento do projeto	X			
Protocolo do estudo, incluindo, se aplicável, os instrumentos de recolha de dados e/ou informação para o participante [a]	X			Protocolo do estudo elaborado de acordo com os requisitos e normas éticas de boas práticas em experimentação com humanos.
Curriculum Vitae abreviado do Investigador Responsável e dos membros da equipa e/ou orientadores [a]	X			Presente
Quando aplicável, documento de Consentimento Informado, elaborado e referenciado de acordo com a alínea [c] abaixo indicada	X			Adequado, um consentimento informado disponível para casos e outro para controlos.
Declaração de Compromisso de Confidencialidade (e/ou Termo de Responsabilidade)	X			Adequado
Quando aplicável, informação sobre financiamento para o cumprimento do projeto, incluindo, se aplicável, cabimento/inscrição no orçamento da Unidade/Serviço em que decorrerá e/ou com fonte de financiamento nacional/internacional	X			Estudo financiado por verbas do orçamento do Instituto de Investigação em Ciências da Vida e Saúde da Universidade do Minho – Escola de Medicina da Universidade do Minho (fundos institucionais), não implicando custos para o Hospital de Braga.
NOTA: O projeto carecerá de Parecer/Autorização ética local das unidades de saúde onde forem realizados os recrutamentos e/ou obtidos os dados clínicos dos pacientes participantes no estudo de investigação.				

[a] Documentos obrigatórios de acordo com as normas orientadoras para submissão de processos a apreciar pelo Conselho de Ética da UMinho.
[b] Documentos obrigatórios de acordo com o funcionamento da Comissão de Ética para a Saúde do Hospital de Braga (CESHB).
[c] Documento de Consentimento Informado, Livre e Esclarecido para Participação em Investigação de acordo com a Declaração de Helsinquia[1], a Convenção de Oviedo[2] e o Regulamento Geral de Proteção de Dados (RGPD)[3]. Guião na elaboração do consentimento informado é disponibilizado pela ARSN[4] e através do "Documento CEIC sobre o Regulamento Geral de Proteção de Dados (RGPD) no contexto da Investigação Clínica"[5].

Acesso aos documentos da alínea c):
[1] http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf
[2] http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf
[3] https://eur-lex.europa.eu/legal-content/PT/TXT/?uri=celex%3A32016R0679
[4] http://www.arsnorte.min-saude.pt/consentimento-informado/
[5] http://www.ceic.pt/documents/20727/0/Documento+CEIC+sobre+o+Regulamento+Geral+de+Prote%C3%A7%C3%A3o+de+Dados+%28RGPD%29_publica%C3%A7%C3%A3o/ced81411-5fe4-46f5-a613-c7c716abbb4b

APPENDIX B

Ethics committee approval – *Hospital de Braga*

PARECER

PROJECTO: Regulação cognitiva durante a tomada de decisão em estudantes de medicina
ENTIDADE FINANCIADORA: Verbas próprias para investigação da Escola de Ciências da Saúde
INVESTIGADOR RESPONSÁVEL: Pedro Morgado, MD; Nuno Sousa, MD, PhD – Professor Catedrático da ECS/Investigador Principal do LA ICVS/3B's, Diretor Centro Clínico Académico-Braga.

O Centro Clínico Académico-Braga (CCAB) manifesta apoio ao projecto supra-referenciado, sob a supervisão científica do Dr. Pedro Morgado, considerando-o uma mais-valia para o desenvolvimento de investigação na área científica em questão. O projeto insere-se no âmbito da investigação em curso no CCAB, e no âmbito da investigação de ponta incentivada pela unidade.

Centro Clínico Académico-Braga

Nuno Sousa
(Diretor, MD, Prof. Cat.)

Hospital Braga

Comissão de Ética para a Saúde

Data: 28 Novembro de 2017

Nossa referência: **150/2017**

Relator: Sara Barroso

Parecer emitido em reunião plenária de 28 de novembro 2017

Nos termos dos Nº 1 e 6 do Artigo 16º da Lei Nº 21/2014, de 16 de Abril, a Comissão de Ética para a Saúde do Hospital de Braga (CESHB) em relação ao estudo **"Self-regulation of anxiety in obssessive-compulsive from the lab to a real life application"**, Estudante de doutoramento/bolseira de investigação de que é investigadora principal Sónia Maria Gomes de Amaral Ferreira do Instituto de Ciências da Vida e Saúde da Escola de Medicina da Universidade do Minho, orientador José Miguel Gomes Moreira Pêgo, Professor associado do Instituto de Ciências da Vida e Saúde da Escola de Medicina da Universidade do Minho e Pedro Ricardo Luís Morgado, Professor auxiliar do Instituto de Ciências da Vida e Saúde da Escola de Medicina da Universidade do Minho:

a) O estudo revela-se pertinente pois prevê a melhoria da qualidade de vida de pacientes obsessivos compulsivos que poderão ser capazes de gerir a manifestação sintomática de forma mais sustentada e ecológica, reduzindo a necessidade de cuidados médicos e mantendo sua privacidade. Os resultados deste estudo poderão representar ainda uma mais valia para aplicação a outros transtornos psiquiátricos também afetados pela ansiedade. Estão definidos os critérios de publicação dos resultados da investigação.

c) Trata-se de um estudo com componente observacional retrospetivo e com intervenção prospetivo. O projeto é organizado em quatro tarefas (Tarefa 1, 2, 3 e 4) que serão realizadas na ICVS e no Hospital de Braga, em colaboração com a Unidade de Psiquiatria e o Centro Clínico Acadêmico (2CA-Braga). O projeto pretende estudar de que forma a autorregulação através da técnica de neuro feedback afeta os sintomas de ansiedade em doentes com obsessão-compulsão

através da análise da atividade neuronal periférica e central. Com o desenvolvimento de modelos computacionais pretende prever a ocorrência de obsessão tendo em conta os níveis de ansiedade. O objetivo a longo prazo do estudo será a criação de um dispositivo móvel portátil que permita a autorregulação sintomática em doentes obsessivo-compulsivos de forma continuada.

b) Prevê-se que o estudo permita o desenvolvimento de estratégias individuais para a autorregulação de sintomas de ansiedade nos doentes com obsessão compulsão. A qualidade de vida dos doentes poderá melhorar através da autorregulação sintomática de forma continuada e num ambiente mais ecológico, podendo reduzir a necessidade de outros cuidados médicos. As colheitas de sangue previstas no protocolo de investigação poderão causar um desconforto temporário aos participantes bem como a realização das aquisições de ressonância magnética e de eletroencefalografia.

d) A aptidão do investigador principal e dos restantes membros da equipa está demonstrada;

e) As condições materiais e humanas necessárias à realização do estudo clínico estão reunidas:

f) O projeto é financiado por uma bolsa de doutoramento da Fundação para a Ciência e Tecnologia (PD/BDE/127839/2016, com a duração de 4 anos), por uma bolsa nacional do Centro Clínico Académico do Hospital de Braga (*Treating refractory obsessive-compulsive disorder using real-time functional magnetic resonance imaging neurofeedback*, duração de 1.5 anos) e por fundos do próprio instituto. A realização do projeto não implica qualquer custo para o Hospital de Braga. Não está contemplado o ressarcimento ou remuneração dos participantes.

g) Serão recrutados no Hospital de Braga quarenta e cinco indivíduos com Transtorno Obsessivo-Compulsivo sendo constituída uma amostra de conveniência não aleatória, abrangendo uma faixa etária de 18 a 40 anos, de acordo com o cálculo amostral. Os pacientes serão diagnosticados de acordo com o quinto Manual Diagnóstico e Estatístico de Transtornos Mentais para resistência ao tratamento (≥ 3 medicamentos em dose adequada por ≥ 12 semanas) e obsessões de contaminação ([Escala 1] Escala Compulsiva Obsessiva Yale-Brown [Y-BOCS] pontuação ≥ 17) 18 para padronizar as características da amostra. O histórico clínico será avaliado , incluindo informação sociodemográfica, início e gravidade da doença e tratamento prévio / atual,

questionários sociodemográficos clínicos e as respostas aos questionários 1 e 2. São critérios de exclusão doenças psiquiátricas ou neurológicas concomitantes, hipertensão, diabetes, hipercolesterolémia, abuso / dependência de substâncias em nos últimos 6 meses (exceto a nicotina / cafeína), ideação suicida aguda, medicamentos (exceto antidepressivos e medicamentos anticoncecionais) ou contraindicações de RMN.

h) Não estão referidas situações de conflito de interesses por parte do promotor ou investigador envolvidos no estudo clínico;

i) O acompanhamento clínico dos participantes está previsto no protocolo de investigação. Os pacientes serão sempre supervisionados por um médico para rastrear complicações putativas. A participação será imediatamente interrompida em caso de reações adversas ou agravamento sintomático e um médico acompanhará os participantes para fornecer os cuidados apropriados. Em caso de descoberta involuntária do projeto com significado clínico putativo, os pesquisadores podem consultar um médico especializado para indicar a melhor solução para o participante.

j) O procedimento de obtenção do consentimento informado, incluindo as informações a prestar aos participantes é adequado e referente a cada uma das etapas que constituem o estudo.

Toda a informação será recolhida e guardada de forma confidencial, anónima e codificada. Não haverá qualquer divulgação ou comunicação de resultados individuais. Os dados recolhidos serão exclusivamente utilizados para este estudo. Todos os contactos serão feitos em ambiente de privacidade e os dados de resultados do projeto serão sempre codificados para proteger a confidencialidade e a privacidade dos participantes. O projeto foi submetido e aceite pela Comissão Nacional de Proteção de Dados (CNPD) tendo sido obtida a Autorização n.º 11736/ 2017. Os dados estarão acessíveis ao Professor coordenador do projeto no ICVS, também médico no Hospital de Braga, que acompanhará os doentes, Pedro Ricardo Luís Morgado.

k) O protocolo de investigação prevê as limitações do estudo. Grupos aleatórios poderão não ser comparáveis quanto à idade, gênero e gravidade da doença, o que será avaliado durante a análise de dados. No caso de incapacidade de encontrar a "impressão digital EEG" na Tarefa 2, serão realizadas adaptações de estímulo. Se as adaptações ainda forem insuficientes, o neuro feedback EEG será baseado em literatura anterior

A avaliação neuro psicológica e clínica pode induzir alterações no estado emocional dos participantes. No entanto, essas avaliações serão realizadas por médicos e psicólogos treinados e experientes para minimizar o desconforto dos participantes. Estão descritos os incómodos possíveis para os doentes e prevista a sua minimização.

Em suma, o estudo cumpre os princípios da Bioética, pelo que a Comissão de Ética para a Saúde do Hospital de Braga nada tem a opor à sua realização.

O Presidente da CESHB

(Dr. Juan Garcia)

Hospital Braga

Comissão de Ética para a Saúde

07 de Agosto de 2019

Refª 111_2019

Relator: Sara Barroso

26/8/19

Parecer emitido em reunião plenária de 10 de julho de 2019

Nos termos dos Nº 1 e 6 do Artigo 16º da Lei Nº 21/2014, de 16 de Abril, em relação ao estudo ***"Alteração nos mecanismos neurobiológicos associados às tomadas de decisão em indivíduos com Perturbação Obsessivo- Compulsiva"***, de que é investigador principal, Maria Beatriz Couto, co investigadores Ana Matilde Gomes, Maria Picó Pérez, Pedro Moreira, Sónia Ferreira, orientador o Professor Doutor Pedro Morgado da instituição, a Comissão de Ética do Hospital de Braga (CEHB) emite o seguinte parecer:

a) O estudo revela-se pertinente na medida em que se propõe investigar a relação da tomada de decisão na Perturbação Obsessiva Compulsiva (POC) e que alterações em termos neurobiológicos é que estarão subjacentes;

b) Trata-se de um estudo prospetivo, que tem como objetivos principais caracterizar as tomadas de decisão nos doentes com POC e compreender, do ponto de vista neuroanatómico e neurofuncional, os padrões de ativação cerebral durante tarefas de tomada de decisão destes doentes.

c) Não estão previstos riscos ou benefícios diretos para os participantes;

d) A aptidão do investigador principal e dos restantes membros da equipa está demonstrada;

e) As condições materiais e humanas necessárias à realização do estudo clínico estão reunidas;

f) Não está prevista a retribuição ou compensação dos investigadores e dos participantes no estudo clínico. O projeto será financiado integralmente por verbas do orçamento do Instituto de Investigação em Ciências da Vida e Saúde da Universidade do Minho – Escola de Medicina da Universidade do Minho (fundos institucionais), não implicando custos para o Hospital de Braga.

g) A população alvo inclui doentes seguidos na consulta externa de Psiquiatria do Hospital de Braga diagnosticados com POC. Os pacientes serão recrutados na consulta de Psiquiatria do Hospital de Braga pelo Prof. Dr. Pedro Morgado. Os doentes serão incluídos no estudo de acordo com os critérios de inclusão e exclusão perfeitamente definidos no protocolo de investigação e que tenham cedido o seu consentimento. Está prevista a inclusão de cerca de 20 doentes.

h) Não são referidas situações de conflito de interesses por parte dos membros da equipa de investigação.

i) O acompanhamento clínico dos participantes em nada será influenciado pela participação neste estudo;

j) O procedimento de obtenção do consentimento informado, incluindo as informações a prestar aos participantes é adequado e contém informação escrita ao participante, em linguagem acessível e clarificadora dos objetivos do estudo, riscos e benefícios da participação, explicitando a inteira liberdade para aceitar ou recusar; e poder, em qualquer momento, anular a decisão de participar – sem que seja pedida justificação – com efeitos imediatos e sob a garantia de não retaliação. Esta informação será cedida em momento prévio à obtenção de Consentimento, onde será explicitada também a utilização de dados pessoais e comunicação ou publicação dos resultados, com garantia de anonimização, sendo que a propriedade dos dados será exclusiva desta entidade. Os doentes serão informados que podem solicitar o financiamento da deslocação (como por exemplo, o parqueamento e a justificação da ausência ao trabalho).

k) Imediatamente antes da avaliação neuro-imagiológica será realizada a colheita das amostras sanguíneas, colhidas por punção venosa periférica com vista a armazenamento (salvaguardada a identificação do doente) e posterior análise bioquímica dos dados previamente indicados. A avaliação bioquímica das amostras sanguíneas requer a recolha dos seguintes parâmetros Contagem de Células Sanguíneas, Cortisol, Hormona de Crescimento, Hormonas da Tiróide (T4 e TSH) e Insulina.

Os participantes incluídos no estudo serão sujeitos a Ressonância Magnética Estrutural e Funcional durante a qual passarão por um período de repouso, um período onde irão realizar a tarefa BART, um período de regulação emocional. Trata-se de paradigmas de tomada de decisão validados, sendo que o teste escolhido não ultrapassa os 90 minutos, podendo ser interrompida a qualquer momento pelo doente se assim o desejar.

A avaliação Clínica e Psicológica serão conduzidas mediante aplicação das seguintes escalas:

- Questionário de Regulação Emocional;
- NEO- FFI;
- OCI-R;
- PSS-10;

Será ainda aplicado um questionário de avaliação de dados sociodemográficos.

Será constituído um grupo controlo com pessoas que não tenham diagnóstico prévio de POC e que realizem as escalas mencionadas anteriormente e não obtenham a pontuação necessária para o diagnóstico desta perturbação. Estes controlos serão escolhidos de acordo com os doentes, ou seja, serão emparelhados um a um para a idade, o sexo e a escolaridade.

Os registos serão anonimizados, atribuindo-se a cada sujeito, no momento da inclusão no estudo, um código de identificação único. Apenas o investigador principal terá acesso à correspondência entre o nome do sujeito e o código de identificação, garantindo, assim, a confidencialidade dos dados dos participantes.

Em suma, o estudo cumpre os princípios da Bioética pelo que a CE HB nada tem a opôr à sua realização.

O Presidente da CESHB

(Dr. Juan R. Garcia)

APPENDIX C

Conference abstracts

1. E-poster – 32nd ECNP Congress - September 2019 - Copenhagen, Denmark

Decreased cognitive flexibility impairs decision-making in obsessive-compulsive disorder – a functional magnetic resonance imaging study

Sónia Ferreira[1,2], Pedro Moreira[1,2], Ricardo Magalhães[1,2], Ana Coelho[1,2], Paulo Marques[1,2], Carlos Portugal-Nunes[1,2], Nuno Sousa[1,2], Pedro Morgado[1,2]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [2]ICVS-3Bs PT Government Associate Laboratory, Braga/Guimarães, Portugal

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts (obsessions) and ritualistic/mental actions intended to diminish the anxiety elicited by obsessions (compulsions). Besides typical symptoms, OCD is also defined by cognitive deficits such as poor response inhibition, attentional deficits, decision-making impairments (e.g. habitual behavior and risk/harm avoidance), and reduced cognitive flexibility [1]. While cognitive regulation of emotions has been extensively studied in OCD [2], [3], the mechanisms of cognitive control of decision-making are still unknown in this disorder. Thus, our goal was to investigate the impact of OCD on the cognitive regulation of reward-related decision-making at behavioral and neural functioning levels.

Heathy (n=14, 9 females/5 males, age 24-58 years) and OCD participants (n=15, 10 females/5 males, age 21-44 years, DSM-IV diagnosis) were included in the study. We used a functional magnetic resonance imaging task where participants had to cognitively upregulate or downregulate their craving before placing a bid to obtain a food item display on a picture. The food pictures (n=150) were displayed during the task under three cognitive regulation conditions: indulge, distance, and natural. Subjects were instructed to try to increase or decreased craving for the indulge and distance conditions, respectively. For the natural condition, we instructed them to allow natural thoughts and feelings about the food. After each cognitive regulation trial, participants had to place a bid for the food item (0, 1, 2, or 3 €). We used a 1.5T Siemens scanner with a 12-channel coil. A T2* weighted echo-planar imaging sequence was acquired at 30° relative to the anterior-posterior commissure. Two statistical models based on repeated measures ANOVA were used to analyze the brain activity differences between groups for cognitive regulation (between-group: group; within-group: cognitive regulation condition) and food valuation during the task (between-group: group; within-group: cognitive regulation condition and valuation score). Cluster

correction was applied for multiple comparisons. Data were analyzed with Statistical Parametric Mapping and JASP.

We found that OCD patients failed to modulate food valuation scores accordingly to the cognitive regulation condition in contrast to healthy participants (group×condition $F_{(2,52)}$=3.5, p=0.036). Moreover, the right temporal gyrus was hypoactivated during cognitive regulation in OCD participants compared to controls ($t_{(27)}$≥3.4, p≤0.001). Furthermore, we found different responses between groups in left frontoparietal regions (inferior frontal gyrus, pre/postcentral gyrus, and insula) and right temporoparietal areas (supramarginal gyrus, angular gyrus, temporal lobe, and inferior parietal lobule) during food valuation (group×valuation $F_{(3,81)}$>5.96, p<0.001).

We concluded that OCD patients have poor cognitive flexibility leading to deficits in reward processing during decision-making. We propose that these results may derive from deficient management of internal states caused by obsessions during cognitive regulation, or from the imbalance in the brain pathways often implicated in compulsive behavior underlying cognitive control and reward-related processing [4], [5]. Our results might guide the development of cognitive strategies to tackle impairments in decision processes in OCD to be incorporated in existing cognitive-behavioral therapies.

[1] E. R. Stern and S. F. Taylor, 2014. Cognitive neuroscience of obsessive-compulsive disorder. Psychiatr. Clin. North Am. 37(3), 337–352.

[2] X. Goldberg *et al.*, 2016. Inter-individual variability in emotion regulation: pathways to obsessive-compulsive symptoms. J. Obsessive. Compuls. Relat. Disord. 11, 105–112.

[3] A. L. Thorsen *et al.*, 2018. Emotion regulation in obsessive-compulsive disorder, unaffected siblings, and unrelated healthy control participants. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 12, 1–9.

[4] C. Xie *et al.*, 2017. Imbalanced functional link between reward circuits and the cognitive control system in patients with obsessive-compulsive disorder. Brain Imaging Behav. 11(4), 1099–1109.

[5] M. M. Vaghi *et al.*, 2017. Specific frontostriatal circuits for impaired cognitive flexibility and goal-directed planning in obsessive-compulsive disorder: evidence from resting-state functional connectivity. Biol. Psychiatry 81(8), 708–717.

2. Poster – 32nd rtFIN Conference - December 2019 - Maastricht, Netherlands

A feasibility study of fMRI neurofeedback for treatment-resistant obsessive-compulsive disorder

Sónia Ferreira[1,2], Maria Picó-Pérez[1,2], Mafalda Sousa[1,2], Rita Vieira[1,2] & Pedro Morgado[1,2]

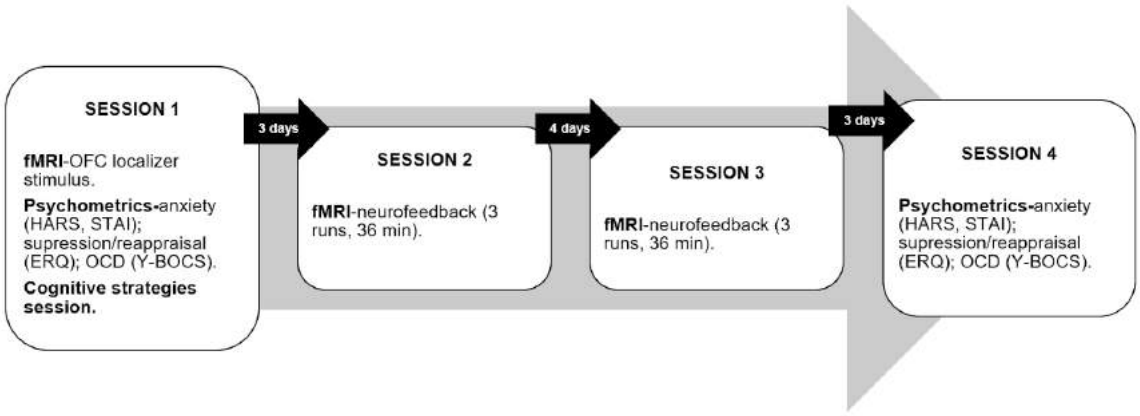
[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [2]ICVS-3Bs PT Government Associate Laboratory, Braga/Guimarães, Portugal

Introduction Obsessive-compulsive disorder (OCD) is a severe condition characterized by recurrent intrusive thoughts (obsessions) and ritualistic actions (compulsions) intended to diminish the anxiety elicited by obsessions. The orbitofrontal cortex (OFC) is one of the main dysfunctional brain regions in OCD, presenting increased levels of activity [1]. First-line treatments for OCD include cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs). However, at least 30% of the patients do not achieve sustained remission after treatment. Invasive neurosurgery and deep brain stimulation might be used in these cases [2]. Neurofeedback is a non-invasive intervention for real-time self-modulation of dysfunctional brain regions. fMRI neurofeedback seems to reduce OCD symptoms [3] but previous studies lack validation with large samples and/or are not controlled. Thus, our project intends to use fMRI neurofeedback with a larger population of treatment-resistant OCD patients using a controlled design (treatment versus sham group). We hypothesize that OCD-related symptoms will decrease after neurofeedback. Here we report our preliminary results from the treatment group.

Materials and Methods

Participants and preparation: Seven OCD participants (age 20-45 years; 5 females) were recruited at *Hospital de Braga* and diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (5th edition), and the Mini-International Neuropsychiatric Interview. The selected patients were diagnosed with treatment resistance (≥3 SSRIs trials at maximum dose for ≥12 weeks [2]). Exclusion criteria were concomitant psychiatric/neurological illness, use of medication (except SSRIs, occasional hypnotic/anxiolytic medication, or birth control drugs), or fMRI contraindications.

General procedure and study design:



Stimulation, task, and instruction: Before neurofeedback, a psychologist explained distancing and reinterpretation strategies to the patients while exemplifying with OCD-related pictures [4]–[6]. Distancing involved emotional detachment from the situation described by the picture and reinterpretation consisted of finding positive aspects for it. Participants were advised to use these tactics during neurofeedback.
OCD-related versus neutral pictures were used to individually localize the OFC region inside the fMRI scanner before neurofeedback. The neurofeedback protocol was designed with the OpenNFT software (http://opennft.org/). OpenNFT performs realignment, reslicing, and spatial smoothing, and the activation maps are estimated with incremental GLM (head motion correction, high-pass 1/128 s, and low-pass Kalman filtering). During neurofeedback sessions, following a text cue, we instructed the participants to regulate the activity of the OFC based on the feedback provided by using the cognitive reappraisal strategies learned. Following each cue, 4 OCD-inducing pictures were shown. Twelve blocks were used per run interspersed with a grey baseline (12min/run). The feedback was continuously provided and estimated based on the percent signal change in the OFC. The feedback values were displayed as the level of transparency of the pictures: if patients were able to decrease the OFC activity, the picture became more transparent (positive feedback); otherwise, the picture became sharper (negative feedback). The neurofeedback stimulus was back-projected on a screen.

Data acquisition: Each participant was scanned on a 3 T MAGNETOM Verio (Siemens Medical Solutions, Germany) using a 20-channels head coil and a T2 weighted multi-band accelerated echo-planar imaging acquisition (44 slices, repetition time 1s, echo time 27ms, resolution $3mm^3$, and 30° orientation relative to the anterior-posterior commissure line).

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to quantify OCD symptoms severity (both obsessions and compulsions), and the Hamilton Anxiety Rating Scale (HARS) was used to measure the severity of anxiety symptoms. State and trait anxiety were also assessed with the State-Trait Anxiety Inventory (STAI). The Emotion Regulation Questionnaire (ERQ) was applied to measure reappraisal and suppression capabilities. Psychometric scales were used before and after the neurofeedback sessions to measure the neurofeedback efficacy.

Data analysis: Psychometric data were analyzed with JASP (https://jasp-stats.org/) with one-sided paired sample *t*-tests ($p < 0.05$ for statistically significant differences).

Results and Conclusions After neurofeedback, OCD severity decreased significantly [Y-BOCS $t(6)=4.0$, $p=0.004$, $d=1.5$]. The obsessions score was significantly lower [$t(6)=7.8$, $p<0.001$, $d=2.9$] and the compulsions score decreased [$t(6)=1.6$, $p=0.084$]. Additionally, anxiety levels were significantly reduced [HARS $t(6)=2.7$, $p=0.019$, $d=1.0$; STAI $t(6)=3.7$, $p=0.005$, $d=1.4$]. The EQR reappraisal score augmented [$t(6)=-1.7$, $p=0.072$] and the suppression score did not change [$t(6)=-0.1$, $p=0.533$]. Moreover, the self-reported neurofeedback success significantly increased from session 2 to 3 [$t(6)=-2.1$, $p=0.040$, $d=-0.8$] while the self-reported task difficulty decreased [$t(6)=-1.7$, $p=0.067$]. In conclusion, fMRI neurofeedback seems to improve the OCD symptomology for treatment-resistant patients. Nonetheless, in the future, our results need to be compared with the sham group to account for putative placebo effects of neurofeedback, and the sample size must be increased.

References

[1] A. L. Thorsen *et al.*, *Biol. Psychiatry Cogn. Neurosci. Neuroimaging*, vol. 3, no. 6, pp. 563–571, Jun. 2018.

[2] M. Gershkovich *et al.*, *Curr. Treat. Options Psychiatry*, vol. 4, no. 4, pp. 357–370, Dec. 2017.

[3] S. Ferreira *et al.*, *Psychiatry Res.*, vol. 272, no. December 2018, pp. 237–245, Feb. 2019.

[4] D. Mataix-Cols *et al.*, *Psychiatry Res.*, vol. 168, no. 3, pp. 238–241, Aug. 2009.

[5] D. Simon *et al.*, *Psychiatry Res.*, vol. 198, no. 1, pp. 81–88, Jun. 2012.

[6] M. Hampson *et al.*, *J. Vis. Exp.*, no. 59, Jan. 2012.

P.406
Hippocampal volume increase in electroconvulsive therapy is independent of amyloid deposition in late-life depression

M. Laroy[1,*], L. Emsell[1,2,3], K. Vansteelandt[1], F.L. De Winter[1,3], A. Dols[4], M. Stek[5], P. Sienaert[6], M. Vandenbulcke[1,3], F. Bouckaert[1,3]

[1] *KU Leuven, Laboratory for Translational Neuropsychiatry, Leuven, Belgium*
[2] *KU Leuven, Translational MRI, Leuven, Belgium*
[3] *UPC Leuven, Old Age Psychiatry, Leuven, Belgium*
[4] *VU Amsterdam, Old Age Psychiatry, Amsterdam, The Netherlands*
[5] *VU Amsterdam, Old Age Psychiatry, Leuven, The Netherlands*
[6] *KU Leuven, Academic Center for ECT and Neuromodulation, Leuven, Belgium*

Background: Hippocampal volumetric changes (HVC) following electroconvulsive therapy (ECT) have been widely reported as a robust phenomenon [1]. The change in volume associated with this neuromodulating agent follows an increase-and-normalization pattern [2,3]. Increased hippocampal [2] and in particular dentate gyrus [3] volumes have been reported immediately after ECT and found to subsequently return to baseline levels within 3 to 6 months after ECT. Furthermore, evidence for the reduction of plasma Aβ40 following ECT alludes to a possible interaction between amyloid metabolism and ECT-related phenomena [4].
Objective: The objective of the study was to explore the effect of amyloid deposition on ECT-related HVC. Given the synaptotoxic effects of amyloid metabolization, we hypothesized (1) that higher amyloid deposition would be associated with smaller hippocampal volume increases from baseline to 1-week after the last ECT, (2) that the 'normalization' of hippocampal volume would be altered by the synaptotoxic effects of amyloid deposition and (3) that greater amyloid deposition is associated with larger hippocampal volume decreases from 1 week after to 6 months after the last ECT.
Methods: In a sample of 34 patients with geriatric depression, structural magnetic resonance imaging was conducted one week before ECT (T1, n =34), one week after (T2, n=28), and six months after the last ECT (T3, n=12). Amyloid imaging using [18F]-flutemetamol positron emission tomography was performed 1 week prior to the ECT course (T1, n =34). Left and right hippocampal volumes were defined manually and were normalized for total intracranial volume [5]. HVC was defined as the percentage change from one time point to another in order to control for interindividual variability. Amyloid-binding was quantified using standardized uptake value ratio (SUVR) in one cortical composite volume of interest. Based on a median-split (SUVR=1.270), the sample was divided into two subsamples (lower vs. higher amyloid deposition) of equal size.
Results: Two outliers were detected based on the standard deviation of HVC and were removed. An ANOVA revealed an effect of low vs. high amyloid deposition on the percentage volume change in the left hippocampus ($F(1,26)=5.107$, $p=.032$) from T1 to T2, but not for the right hippocampus ($F(1,26)=1.262$, $p=.272$). A posthoc test revealed that the higher amyloid group had a larger increase in hippocampal volume from T1 to T2 in the left hippocampus compared to the amyloid-low group. However, after controlling for age and the number of ECT sessions via multiple linear regression, the effect of low vs. high amyloid deposition was no longer significant (= 126.13, $t=1.78$, $p=.088$). No significant effect of amyloid binding with left or right hippocampal volume change was detected from T2 to T3.
Conclusion: In our sample, contrary to our hypotheses, we found limited evidence for an effect of amyloid deposition on ECT-related HVC one week and 6 months after treatment. Age and number of ECTs may mediate the effect on HVC and should be accounted for in future analyses.

Disclosure statement: Mathieu Vandenbulcke was supported by the Research Foundation-Flanders (Fonds Wetenschappelijk Onderzoek) Project G.0746.09. This study was also supported by the Sequoia Fund, KU Leuven. The FWO had no further role in study design, collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the paper for publication. For the remaining authors no other sources of funding were declared.

References

[1] Takamiya, A., Chung, J.K., Liang, K., Graff-Guerrero, A., Mimura, M., Kishimoto, T., 2018. Effect of electroconvulsive therapy on hippocampal and amygdala volumes: systematic review and meta-analysis. Br. J. Psychiatry 212, 19-26.
[2] Bouckaert, F., Dols, A., Emsell, L., De Winter, F.-L., Vansteelandt, K., Claes, L., Sunaert, S., Stek, M., Sienaert, P., Vandenbulcke, M., 2016. Relationship Between Hippocampal Volume, Serum BDNF, and Depression Severity Following Electroconvulsive Therapy in Late-Life Depression. Neuropsychopharmacology 41, 2741-2748.
[3] Takamiya, A., Plitman, E., Chung, J.K., Chakravarty, M., Graff-Guerrero, A., Mimura, M., Kishimoto, T., 2019. Acute and long-term effects of electroconvulsive therapy on human dentate gyrus. Neuropsychopharmacology 1-7.
[4] Yamazaki, C., Tamaoki, T., Nunomura, A., Tamai, K., Yasuda, K., Motohashi, N., 2017. Plasma Amyloid- β and Alzheimer's Disease-Related Changes in Late-Life Depression. J. Alzheimer's Dis. 58, 349-354.
[5] Jack, C.R., Twomey, C.K., Zinsmeister, A.R., Sharbrough, F.W., Petersen, R.C., Cascino, G.D., 1989. Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. Radiology 172, 549-554.

doi: 10.1016/j.euroneuro.2019.12.103

P.407
Magnetic resonance imaging-based neurofeedback improves obsessive-compulsive symptomatology

S. Ferreira*, M. Picó-Pérez, M. Sousa, R. Vieira, P. Morgado

Life and Health Sciences Research Institute ICVS- School of Medicine- University of Minho, Neurosciences Research Domain, Braga, Portugal

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts (obsessions) and ritualis-

tic actions (compulsions) intended to diminish the anxiety elicited by obsessions. The orbitofrontal cortex (OFC) is one of the main dysfunctional brain regions in OCD, typically showing increased activity [1]. First-line treatments for OCD are cognitive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs). However, at least 30% of the patients do not achieve remission after treatment. Neurosurgery and deep brain stimulation might be used in these cases [2]. Neurofeedback consists of non-invasive real-time self-modulation of dysfunctional brain regions. Functional magnetic resonance imaging (fMRI) neurofeedback seems to lessen OCD symptoms [3] but previous studies lacked validation with large samples and/or were not controlled.

Our project intends to use fMRI neurofeedback with a larger population of treatment-resistant OCD patients using a controlled design (treatment versus sham). We hypothesize that OCD-related symptoms will decrease after neurofeedback. Here we report our preliminary results from the treatment group.

OCD participants (n=8; 20-45 years; 6 female) were recruited at Hospital de Braga (DSM-5 diagnosis) and were included if they exhibited treatment resistance ($\geq$3 SSRIs trials at maximum dose for $\geq$12 weeks [2]). Exclusion criteria were concomitant psychiatric/neurological illness, use of medication (except SSRIs or anxiolytic medication), or fMRI contraindications. We used a longitudinal design with one fMRI session before and after neurofeedback and two fMRI sessions of neurofeedback (36 min/day). OCD-related [4,5] versus neutral pictures were used to individually localize the OFC region. During the neurofeedback sessions, while visualizing OCD-inducing pictures, we instructed the participants to regulate the activity of the OFC based on the feedback provided, using reappraisal strategies trained earlier. The feedback was presented continuously based on the OFC percent signal change and it was displayed as the transparency of the pictures (if the OFC activity decreased, the picture became more transparent; OpenNFT software). Participant were scanned on a 3T Siemens MAGNETOM Verio using a 12-channels head coil and a T2 multi-band accelerated echo-planar imaging acquisition. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was applied for OCD severity, and the Hamilton Anxiety (HARS) and Depression (HDRS) Rating Scales were used to measure anxiety and depression scores, respectively, before and after neurofeedback. Psychometric data were analyzed with one-sided paired sample t-tests (JASP). We also assessed within-subject changes in resting-state functional connectivity after neurofeedback (CONN toolbox 18b, SPM 12; ICA analysis, 40 components; ANOVA with FDR correction $p<0.05$). Neuroimaging data were preprocessed with the fmriprep pipeline.

After neurofeedback, OCD severity decreased significantly ($t(7)=4.36$, $p=0.002$, $d=1.54$). The obsessions score was significantly lower ($t(7)=4.48$, $p=0.001$, $d=1.69$), and the compulsions score decreased (not significantly; $t(7)=1.83$, $p=0.055$, $d=0.65$). Additionally, anxiety ($t(7)=3.18$, $p=0.008$, $d=1.13$) and depression ($t(7)=1.95$, $p=0.046$, $d=0.69$) levels were significantly reduced. Functional connectivity did not change significantly after neurofeedback. fMRI neurofeedback seems to improve the symptomatology of treatment-resistant OCD patients. This improvement did not correspond to alterations in functional connectivity possibly due to reduced statistical power from the small sample size. Thus, these results need to be compared with the sham group to account for putative placebo effects, and the sample size must be increased.

References

[1] Thorsen, A.L., et al., 2018. Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-analysis of 25 Functional Neuroimaging Studies. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3 (6), 563-571.

[2] Gershkovich, M., Wheaton, M.G., Simpson, H.B., 2017. Management of Treatment-Resistant Obsessive-Compulsive Disorder. Curr. Treat. Options Psychiatry 4 (4), 357-370.

[3] Ferreira, S., Pêgo, J.M., Morgado, P., 2019. The efficacy of biofeedback approaches for obsessive-compulsive and related disorders: A systematic review and meta-analysis. Psychiatry Res 272, 237-245.

[4] Simon, D., Kischkel, E., Spielberg, R., Kathmann, N., 2012. A pilot study on the validity of using pictures and videos for individualized symptom provocation in obsessive-compulsive disorder. Psychiatry Res 198 (1), 81-88.

[5] Hampson, M., et al., 2012. Real-time fMRI Biofeedback Targeting the Orbitofrontal Cortex for Contamination Anxiety. J. Vis. Exp. this issue.

doi: 10.1016/j.euroneuro.2019.12.104

APPENDIX D

Additional work

1. **Preprint - medRxiv – May 2020**

   Link : https://doi.org/10.1101/2020.04.28.20080671

Protective elements of mental health status during the COVID-19 outbreak in the Portuguese population

Pedro Silva Moreira[1,2,3], Sónia Ferreira[1,2], Beatriz Couto[1,2], Mafalda Machado-Sousa[1,2], Marcos Fernández[1,2], Catarina Raposo-Lima[1,2], Nuno Sousa[1,2], Maria Picó-Pérez[1,2*], Pedro Morgado[1,2*]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; 2ICVS/3B's; [2]PT Government Associate Laboratory, Braga/Guimarães, Portugal; [3]Psychological Neuroscience Lab, CIPsi, School of Psychology, University of Minho, Braga, Portugal; *Equal contribution

Abstract

The outbreak of COVID-19 might produce dramatic psychological effects on the individuals' life. In this study, we aimed to explore the elements that may reduce the negative effects on mental health of the quarantine period imposed by most governments during this worldwide crisis. We conducted an online survey to evaluate demographic, lifestyle and mental health variables in the Portuguese population. We observed that factors related with living conditions, maintaining the work either online or in the workplace, frequency of exercise and absence of a previous psychological or physic disorders are protective features of psychological well-being (anxiety, depression, stress and obsessive-compulsive symptoms). Finally, the individuals previously receiving psychotherapeutic support exhibited better psychological indicators if they did not interrupt the process as a consequence of the outbreak. Our results indicate that the practice of physical exercise, reduced consumption of COVID-19 information and the implementation of remote mental healthcare measures might prevent larger impacts on mental health during the COVID-19 outbreak.

2. Manuscript submitted for publication – August 2020

A wakeup call for burnout? A national survey of Portuguese physicians during the COVID-19 outbreak

Sónia Ferreira[1,2], Mafalda Machado-Sousa[1,2], Pedro Silva Moreira[1,2,3], Nuno Sousa[1,2], Maria Picó-Pérez[1,2], Pedro Morgado[1,2]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; [2]ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal; [3]Psychological Neuroscience Lab, CIPsi, School of Psychology, University of Minho, Braga, Portugal

Abstract

The novel coronavirus disease 2019 (COVID-19) outbreak has put a lot of physical and psychological pressure on healthcare professionals, including physicians at the frontline. Thus, evaluating the mental health status of physicians during the current pandemic is important to define future preventive guidelines from healthcare stakeholders.

In this study, a national survey was applied to infer differences in the mental health status (depression, anxiety, stress, and obsessive-compulsive symptoms) between Portuguese physicians working at the frontline of COVID-19 and other physicians that were not working at the frontline. Moreover, we explored the influence of several sociodemographic factors on mental health variables (age, sex, living conditions, and household composition). A representative sample of 420 participants based on age, sex, and geographic region was analyzed (200 participants in the frontline group and 220 in the control group).

Our results showed that being female and working at the frontline were found as potential risk factors for stress. Additionally, younger physicians have higher levels of stress. In contrast, having a house with green space was a potential beneficial factor for stress and anxiety. Despite the study cross-sectional design, our findings point to the necessity of applying protective mental health measures for physicians to avoid long-term effects of stress such as burnout.