Universidade do Minho
Escola de Medicina

Janny Adelaide da Conceição Matuele

Functional Brain Correlates of Cognitive and Affective Impairments in Patients with Paranoid Schizophrenia

Correlatos Cerebrais Funcionais de Deficiências Cognitivas e Afetivas em Pacientes com Esquizofrenia Paranoide

agosto de 2017

NORTE2020 PORTUGAL 2020 UNIÃO EUROPEIA Fundo Europeu de Desenvolvimento Regional

Cofinanciado por:
COMPETE 2020 PORTUGAL 2020 UNIÃO EUROPEIA Fundo Europeu de Desenvolvimento Regional FCT Fundação para a Ciência e a Tecnologia

alumni medicina UNIVERSIDADE DO MINHO
ICVS Life and Health Sciences Research Institute Instituto de Investigação em Ciências da Vida e Saúde
2CABraga

UMinho | 2017 Janny Adelaide da Conceição Matuele Functional Brain Correlates of Cognitive and Affective Impairments in Patients with Paranoid Schizophrenia

Universidade do Minho
Escola de Medicina

Janny Adelaide da Conceição Matuele

Functional Brain Correlates of Cognitive and Affective Impairments in Patients with Paranoid Schizophrenia

Correlatos Cerebrais Funcionais de Deficiências Cognitivas e Afetivas em Pacientes com Esquizofrenia Paranoide

Dissertação de Mestrado
Mestrado em Ciências da Saúde

Trabalho efetuado sob a orientação do
Professor Doutor João Miguel Seiça Bessa Peixoto
e do
Professor Doutor António Pacheco Palha

agosto de 2017

Acknowledgements

The work presented in this thesis was performed in the Life and Health Sciences Research Institute (ICVS), University of Minho. Financial support was provided by Alumni Medicina, under the support of the project "Unrevealing the neurobasis of the negative symptoms of schizophrenia: a novel translational approach".

“A sabedoria é suprema; portanto, adquire a sabedoria. Sim, com tudo o que possuis adquire o entendimento. Estima-a, e ela te exaltará, abraça-a, e ela te honrará. Ela dará à tua cabeça uma grinalda de graça e uma coroa de glória te entregará.”

Bíblia Thompson. Provérbio 4:7-9

Agradecimentos

Em primeiro lugar, a Deus pela sua soberania na minha vida e por ter colocado pessoas tão lindas e importantes em toda a minha existência para me servirem de verdadeiros mestres e pilares**.**

Ao Professor Doutor João Bessa Peixoto, primeiro agradecer pela oportunidade que me ofereceu para participar neste projeto, sabendo de antemão da minha paixão pela imagiologia e do meu pouco conhecimento sobre o assunto. Muito obrigada pela disponibilidade, apoio, boa disposição e amizade. Ouvi muitas vezes palavras de conforto como "Calma, tem tempo para tudo, isso vai dar uma publicação numa dessas revistas."

Ao Professor Doutor António Pacheco Palha, pai da psiquiatria e saúde mental em Moçambique, pelo suporte e amizade, instrumento que Deus usou para materialização desta obra, o meu muito obrigado. Agradecer ainda pelos ensinamentos e pela disponibilidade em ensinar.

À Professora Doutora Joana Palha, por criar condições para que tivéssemos a oportunidade para frequentar o curso nesta escola e ainda pelo apoio e fortalecimento nos momentos de fraqueza.

À Professora Doutora Ana João, que me incentivou a decidir por este tema, mostrando de forma prática que seguir o que mais gostamos é o que mais conta para vida, o meu muito obrigada pelo apoio e carinho.

Ao grupo das Neurociências, em especial ao Carlos Portugal Nunes pelo apoio prestado nos maus e bons momentos nesta academia. A brincar sempre dizias "Eu sou mais que um pai para ti". De facto, o foste. Muito obrigada por me ter segurado pela mão para me instruir em todo o caminho que devia andar nesta nova carreira de investigadora que decidi abraçar. À Joana Reis, por todo o apoio e disponibilidade que me concedeu, a maneira dura e amável que criticava alguns aspectos "Depois de enumerar uma data de aspetos errados da tese, conseguia dizer no final o resto está tudo bem". À Teresa Castanho e à Liliana Amorim, pelos ensinamentos e apoio moral, o meu muito obrigada. Aos que carinhosamente apelidei de "meninos da neuroimagem", sem os quais não teria sido possível a realização deste projeto, Pedro Moreira, Ricardo Magalhães e Paulo Marques, o meu muito obrigada.

Á Sónia Ferreira, pela disponibilidade que teve em ler e corrigir o meu trabalho. Contigo aprendi muito, foram críticas muito duras que vou levar para vida, obrigada por ter cruzado o meu caminho.

À Helena Mendonça, que carinhosamente apelidei de minha psicóloga preferida. O meu muito obrigada pelo apoio, carinho e atenção prestados, sobretudo nos momentos finais e mais difíceis da tese.

Ao Doutor João Palha, pelo carinho, disponibilidade e pelos ensinamentos no dia a dia no contexto de psiquiatria. É para mim um grande mestre, obrigada por despertar em mim a paixão pela arte em observar doentes.

À Dona Conceição, a quem carinhosamente chamo de mãe branca. Muito obrigada pelo apoio e cuidado.

Ao Ministério da Saúde de Moçambique, em especial Dra. Lídia Gouveia pelo apoio e persistência e por ter dado muito de si para que eu pudesse ser beneficiada por este projeto de formação. O meu muito obrigada.

Aos meus colegas, "irmão das trincheiras", Aníbal, Domingas e Rogério, sem dúvida hoje testifico o verso bíblico que diz que há amizades que superam os laços de sangue. O meu muito obrigada por tudo.

A toda a minha família,

Ao meu marido, a quem eu dedico esta tese, pois nunca vi alguém se sacrificar tanto para satisfazer o desejo de sua amada, foi sem dúvida umas das maiores declarações de amor que já vi e vivi.

Aos meus filhos, Luna e Yago: Filhos, na tradição africana, os filhos são a riqueza dos pais e vocês, de facto, o são para mim, não tenho como descrever o amor que sinto por vocês e acima de tudo só Deus para dar a compreensão e a maturidade que tiveram neste período em que estive ausente. Obrigada por tudo. A mãe amo-vos demais.

Gostaria também de expressar o meu amor e apreço pela minha mãe, Palmira Matuele. Obrigado por me ensinar a ser persistente face às dificuldades e por transmitir-me um sentimento de confiança que me ajudou a acreditar que posso ter sucesso seguindo os meus sonhos. Eu te amo tanto.

À minha Irmã Desireé Matuele, por ser um exemplo de força e carácter e um dos meus mais sólidos pilares.

Não quero deixar de lado os meus outros irmãos e cunhados. A cada um de vós, que sempre me incentivaram a caminhar na busca pelo conhecimento. O meu muito obrigada.

À Naira Biquiza, Vanize Manjate, Ângela Afuale e Yolanda Paulo, o meu muito obrigada pelas orações e pelo apoio incondicional prestado. Pude finalmente entender o verdadeiro sentido da palavra amizade. Não importa a distância muito menos o toque físico. Espero saber retribuir este lindo gesto e cada palavra de consolo e ânimo que me dedicaram.

Abstract

Negative symptoms have been identified as the major cause of overload in schizophrenia, despite recent advances in treatment. Schizophrenic patients (SZP) present cognitive and affective alterations that have greater severity in the male gender. Previous studies showed that patients with schizophrenia have impaired neural connectivity with less activated complex functional networks when compared to the healthy population. These functional correlates are not well studied, specifically in the association with empathy and cognition. This study aims to investigate the functional brain correlates of cognitive and affective impairments in male SZP and its correlation with psychometric measures.

A sample of 12 male patients with Paranoid Schizophrenia, followed in the Department of Psychiatry in *Hospital de Braga*, and 6 healthy volunteers from the general population were invited to participate in the study. The psychopathological expression of the disorder was assessed with the Positive and Negative Syndrome Scale (PANSS) and empathy was evaluated using the Interpersonal Reactivity Index (IRI). Task-based functional Magnetic Resonance Imaging (fMRI) and resting-state fMRI were used to obtain the brain activation profile of the subjects.

Our results suggest that patients with schizophrenia display significant difficulties to correctly understand and to deal with emotions and suffering of other people. Importantly, these impairments are related to specific functional brain correlates: (1) negative stimuli are associated with higher activation of the fronto-parietal-occipital and limbic regions; (2) the impairments in the expression of compassion is associated with the activation of the medial prefrontal cortex, a region involved in emotional regulation.

Our findings demonstrate a clear association between the expression of negative symptoms in schizophrenia and abnormal activation of cortical-basal circuits such as basal ganglia–thalamostriatal projections and the thalamic–cortical–striatal functional loop, involved in dopaminergic pathways. However, further studies will be necessary for a better characterization of this phenomenon. Importantly, these findings could pave the way for innovative approaches to the treatment of this chronic and disabling psychiatric disorder.

Keywords: Schizophrenia, Resting-state, DMN, fMRI, Empathy, Functional connectivity, IRI, IAPS

Resumo

Apesar dos avanços recentes no tratamento da esquizofrenia, os sintomas negativos são apontados como a principal causa de sobrecarga em pacientes esquizofrénicos. Estes sintomas abrangem alterações cognitivas e afetivas que se manifestam com maior gravidade no género masculino. Alguns estudos mostram que estes pacientes têm uma conectividade neuronal mais diversificada, porém reduzida, e associada a uma configuração de redes funcionais complexas menos ativadas em comparação com a população saudável. Apesar de existirem diversos estudos na sintomatologia positiva (alucinações e delírios), os correlatos funcionais da empatia e cognição não estão devidamente estudados. Este estudo tem como objetivo investigar os correlatos funcionais dos défices cognitivos e afetivos em pacientes esquizofrénicos do sexo masculino e correlacionar com o Índice de Reatividade Interpessoal (IRI) e com a Escala dos Sintomas Positivos e Negativos (PANSS).

Uma amostra de 12 pacientes do sexo masculino com esquizofrenia paranoide, seguida no Departamento de Psiquiatria do Hospital de Braga, e 6 voluntários saudáveis da população geral participaram neste estudo. A expressão psicopatológica da doença foi avaliada com a PANSS e a empatia com o IRI. A ressonância magnética funcional (fMRI) baseado em tarefas e o fMRI de estado de repouso foram utilizados para obter o perfil de ativação cerebral dos sujeitos.

Os nossos resultados sugerem que os doentes com esquizofrenia apresentam dificuldades significativas para entender corretamente e lidar com as emoções e o sofrimento de outras pessoas. Estas deficiências estão relacionadas com correlatos cerebrais funcionais: (1) estímulos negativos estão associados a uma maior ativação das regiões fronto-parietal-occipital e límbicas; (2) os comprometimentos na expressão da compaixão estão associados à ativação do córtex pré-frontal medial, uma região associada à regulação emocional. Os nossos achados demonstram uma clara associação entre a expressão de sintomas negativos na esquizofrenia e a ativação anormal dos circuitos basais corticais, como as projeções dos gânglios da base-talamo-estriatal e o ciclo funcional talamo-cortical-estriatal, envolvido em circuitos dopaminérgicos. Novos estudos serão necessários para uma melhor caracterização deste fenómeno. Estas descobertas poderão abrir caminho para abordagens inovadoras no tratamento desta perturbação.

Palavras-chaves: Esquizofrenia, Estado de repouso, DMN, fMRI, Empatia, Conectividade funcional, IRI, IAPS

Index

Table index

Figure index

Abbreviations list

APA	American Association of Psychiatry
BOLD	Blood Oxygen Level Dependent
ECN	Executive Control Network
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CID	International Classification of diseases
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
FA	Flip Angle
fMRI	Functional Magnetic Resonance Imaging
GLM	General Linear Model
HC-DLPFC	Hippocampus-Dorsolateral Prefrontal Cortex
ICD	International Classification of Diseases
IAPS	International Affective Picture System
IRI	Interpersonal Reactivity Index
ITI	Interstimulus Intervals
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NMDA	N-methyl D-aspartate
PANSS	Positive and Negative Syndrome Scale
RSNs	Resting State Networks
rs-fMRI	Resting State Functional Magnetic Resonance Imaging
SRT	Selective Reminding Test
SZP	Schizophrenic Patients
SN	Salience Network
TE	Echo Time
TR	Repetition Time
WM	White Matter

INTRODUCTION

1.1. Schizophrenia over the years

Schizophrenia has been known for centuries [1] and is a complex neurodevelopmental psychiatric disorder of unknown etiology involving genetic and environmental interactions [2]. In the nineteenth century, European psychiatrists began to describe a disorder of unknown cause presenting a negative prognosis and a progressive deterioration [1]. The Austrian psychiatrist Bénédict Augustin Morel (1809-1873) described for the first time the disease and named it "dementia praecox" [1, 3]. Kahlbaun, in Germany (1863), appointed the term Catatonia [4] and his disciple Ewald Hecker (1843–1909) described it as Hebephrenia [5, 6]. Nevertheless, it was the German psychiatrist Emil Kraepelin (1856-1926) who integrated those four clinic concepts in the same nosological group [3, 5]. Kraepelin described it as "early dementia", because it presents similar characteristics to dementia, although it arises at the beginning of adulthood. Kraepelin did not give etiological significance to the clinical subtypes, preferring to give a unitary clinical meaning, instead of a multiplicity of diseases within the same group [1]. In 1911, the Swiss psychiatrist Eugen Bleuler introduced the term schizophrenia [7] (from the Greek "*shezein"* meaning split and "*pherenó's"* thought), because he felt that the term used by Kraepelin did not fully describe what actually happened in the disease [2, 3]. The scientist believed that there is a division of the mind at different points which results in a personality fragmentation into several different types, which is why the term was proposed in the plural "schizophrenias", clearly showing that many diseases end up being part of this group [3], contradicting the unitary view of Kraepelin [2, 3]. He also recognized that the subtypes, hebephrenic, paranoid, and catatonic, are not natural nosological entities[1]. However, it was only in 1952 that the Diagnostic and Statistical Manual of Mental Disorders (DSM) accepted the term and incorporated it in its entirety, leaving behind the term dementia Praecox. [3, 7]

1.2. Psychopathology of schizophrenia

The psychopathology of schizophrenia is diverse, which is why we cannot find a pathognomonic sign or symptom of the disease. There are variability and evolution throughout the progression of the disease [8, 9]. Symptoms affect the form and content of the individual's thought, perception, cognition, affection, and behavior, which leads to

a change in the personality of the individual with consequent loss of contact with reality [10]. In fact, the disorder impairs the interpersonal and social relationships.

Bleuler organized the type of symptoms in order of importance, classifying as fundamental or primary those that constitute the signs of chronicity of the disease, namely ambivalence, autism, disturbance of association of ideas, and affection (the 4 A's). These signs and symptoms appear late and remain throughout the disease [2, 11]. Additionally, Bleuler considered the signs or symptoms that are revealed first and prevail in the phase of worsening of the disease as accessory, namely, hallucinations and delusions [3].

The psychopathological definition of schizophrenia evolved over the years and had a great contribution from the German psychiatrist Kurt Schneider. Schneider sought to describe the clinical profile of the disease according to the order of appearance of the symptomatology [2]. He placed as first order signs the ones with greater contribution to the diagnosis in the acute phase: delusions, altered thinking, audio-visual hallucinations, somatic hallucinations, feelings, urges, and acts lived as being provoked or influenced by an external agent [2, 10]. Alteration of perception, delusional ideas, perplexity, mood swings, feelings of emotional blunting, or empathy were considered signs of second order, which seem to be a consequence of first order symptoms [2, 10, 11]. Empathy is the symptom that most challenges the health professionals during treatment, deteriorating the patient's condition through the reduction of communication, socialization capacity, and motivation [9].

Today, the classifications of schizophrenia, including the International Classification of Diseases (ICD) and the DSM, include the positive symptoms defined by Schneider, which appear in the early stage of the disease (hallucinations, delusions, and disorganized thinking) [12], and negative symptoms defined by Bleuler (isolation, mutism, anhedonia, empathy or affective blunting, and impoverishment of the shares reaching catatonia), also called twilight by Kraepelin, and characterized by a later appearance, setting the severity of the disease [2, 13, 14]. However, in the new classification proposed by the American Psychiatry Association (APA), DSM-V 2013, the emphasis given by Schneider to the first-order diagnostic criteria was overlooked [15], leaving behind the symptomatic three-dimension: psychotic (hallucinations and delusions), disorganized ideas, and negative symptoms, since these are also found in other disorders [12, 15, 16]. The objective in the DSM-V changes was to observe the symptoms reported by the patient and identifying the severe ones. Another alteration is the elimination of the subtypes of schizophrenia

(catatonic, disorganized, paranoid, undifferentiated, and residual) due to their low diagnostic stability, low reliability, and low validity [12, 15, 16].

1.3. Classification of symptoms in schizophrenia

For a better characterization of the disorder, the symptomatology of schizophrenia is currently classified into three main categories:

1.3.1. Positive symptoms

Positive symptoms, which arise mainly in the acute phase of the disorder, include delusions, hallucinations, and behavioral changes [2]. The delusional symptoms present diverse subtypes, ranging from persecution, threat, omnipotence, catastrophe, mystic, religious, and sexual [11]. Hallucinations can affect the different senses (auditory, visual, tactile, olfactory, and, less frequently, kinesthetic) [2, 17]. Audio-verbal hallucinations are the most frequent. This type of hallucinations can range from threats to the patient or their close ones, hallucinations of pejorative nature, or voices of command that can give orders that jeopardize their lives and those of others [11, 18]. Behavioral changes can vary from aggression, isolation, or bizarre attitudes manifested in social and altered hygiene behavior [2, 17].

1.3.2. Cognitive symptoms

SZP present diverse cognitive deficits mainly manifesting in verbal memory, vigilance, attention, working memory, intelligence, language, and executive functions [19]. These symptoms are present during disease progression, posing a great challenge to the treatment since improvements in negative and positive symptoms do not imply improvements in cognition[20]. Studies show that the brain areas responsible for cognition include the prefrontal cortex [21] and the temporal lobe [19]. About 70 % of these patients present a decreased cognitive function at the onset of the disease and some of them will present deterioration over time [2, 19]. Studies have shown that children who came to develop the disease already presented deficits in cognition [22], mainly in verbal comprehension, attention, and working memory [19].

1.3.3. Negative symptoms

The negative symptoms accompany the disease evolution and reflect the deterioration of emotions, motivation, speech, thoughts, and interpersonal relationships [2]. At this stage, the patient presents anhedonia, showing little care for the physical aspect and personal hygiene [11]. The spontaneity of communication is lost due to the poor content of thoughts [23].

Schizophrenia comprises impairments in empathy and the development of affective blunting [2, 23]. Empathy is the ability to understand the desires, ideas, and actions of others and the aptitude to imagine oneself in the other's place [24, 25]. The impairments in empathy are especially challenging during the medical treatment because they are associated with executive deficits, impaired working memory, slowed information processing, and episodic memory deficits [26]. Recent studies showed that some brain areas respond to the visualization of different human figures, possibly being involved in empathy manifestation [27, 28]. Moreover, questionnaires have been developed to measure individual differences in the empathy trait, namely the Interpersonal Reactivity Index (IRI) [29]. IRI is currently used to examine clinical conditions that affect social-emotional functioning such as paranoid schizophrenia [25] and Parkinson's disease, providing a useful basis for comparison [30]. Individuals with higher IRI scores show increased activation of the anterior insula and frontal operculum when observing facial expressions. People with a high IRI score show a rapid and strong recovery from stress in response to positive images (love and family) after experiencing emotions that induce discomfort. Furthermore, people who have a high IRI score show better emotional stability [30].

1.4. Epidemiology

Schizophrenia is distributed worldwide without gender, race, and social class predominance [31]. The worldwide prevalence of schizophrenia is around 45 cases per 1000 inhabitants, and the risk of developing the disease throughout life is 0.7 % [2, 11]. Nowadays, schizophrenia affects 0.7 to 1.0 % of the world population [32]. In Portugal, schizophrenia is the third more frequent mental disorder with a rate of 2.8 % [33]. The

annual costs supported by the European social and health system are close to 35.2 million euros [34].

Schizophrenia has a great impact on the patient's professional and social relationships [35], resulting in dramatic consequences that affect the patients daily activities. In fact, approximately 70 to 92 % of SZP are unemployed and have thirteen times more probability of a suicide attempt [35]. Epidemiological studies show that life expectancy for patients with schizophrenia is 20 % lower than the general population ranging from 7.8 to 22.5 years [36], with 2/3 dying of natural causes and 1/3 for non-natural causes [37]. The causes of natural death, most commonly associated with disease, are cardiovascular pathologies [38], where smoking is the main risk factor. In fact, 75 % of SZP are smokers [38]. Furthermore, dyslipidemia and serum elevation of triglycerides, associated with the use of typical antipsychotics that alter the lipid metabolism, contribute to obesity, increasing the chance of having cardiac pathology [39]. Suicide is the most common of the unnatural causes and it is estimated that around 38 % of SZP commit suicide [40, 41]. One-third of the mortality in SZP is attributed to suicide, although in some studies it reached 50 %, meaning that the risk is twelve times higher in these patients than in the general population [38, 41]. It was also reported that 1/3 of the suicides occur within the first months of hospital discharge and 1/3 during hospitalization [38].

1.4.1. Gender differences in schizophrenia

The prevalence of schizophrenia among men and women is similar, but the onset of the disease is five years earlier in men when compared to women [35, 42, 43]. At the onset, the severity is higher in men. However, after 45 years of age, the severity becomes higher in women with hormonal changes, justifying why several studies suggest the hormonal protection for females (estrogen hypothesis) [35, 44, 45]. Additionally, women are more sensitive to antipsychotics when compared to men [35, 46, 47] subscribing the idea that hormones may influence the treatment [42, 48]. Kulkarni et al. [49, 50] showed that antipsychotic drugs were more effective in females due to the association with estradiol hormone, which grounded the hypothesis of severity in the male gender. Studies also showed that there is a variation of symptomatology during periods with a hormonal fluctuation [46, 48, 51]. During the hormonal cycle, women have a reduction of the symptomatology [51], which suggests a hormone-protective process [48]. Therefore, in humans, estrogen seems to be neuroprotective, capable of inducing regeneration, and a

suppressor of glutamic glycogenic stress. Thus, this hormone contributes to the prevention of cortical neurodegeneration in schizophrenia [46, 48].

1.5. Etiology

1.5.1. Genetic theory

Schizophrenia has a genetic component with a heritability of 80 % [52]. The family history of schizophrenia is a risk factor for the development of disease and first-degree relatives are at increased risk. The concordance rate for schizophrenia in homozygous twins is 50 % and in dizygotic twins is 12-15 % [33, 53, 54].

Recent studies have shown that there are numerous genes, proteins, mRNAs (messenger Ribonucleic Acid), miRNAs (micro Ribonucleic Acid), and lncRNAs (long-term Codon Ribonucleic Acid) associated with mental disorders [54]. In this way, several cellular mechanisms ranging from cell migration, cell survival, and neurogenesis are involved in schizophrenia, which constitutes a challenge for the diagnosis of the disease [53, 54].

SZP have gene mutations that affect neurodevelopment, resulting in a poor neuronal communication that manifests in the early adulthood, at the disease onset age [55]. This explains why neurodevelopment errors occurring through normal simple nucleotide polymorphisms and copy number variants within the population, or by insertion/deletion type mutations can alter single or multiple cell or metabolic processes [55, 56]. In addition, a larger number of copy number variants were identified in SZP [56], which may ultimately lead to the manifestation of the symptomatology of the disease.

1.5.2. Neurodevelopment theory

Several studies suggested that changes during intrauterine and postnatal development may interfere with the development of certain brain structures, favoring the susceptibility for schizophrenia [54, 55]. Furthermore, complications during childbirth and premature birth are thought to cause lesions in the hippocampus and cerebral cortex by hypoxic mechanisms [57, 58], increasing the risk of development of psychiatric disorders, including schizophrenia [55]. In addition, aspects such as nutritional deficiency during pregnancy, which results in a deficiency of oxygen, iodine, iron, and glucose for the fetus, may be involved in poor Central Nervous System (CNS) maturation [57]. Moreover,

pathologies during the first trimester of pregnancy (e.g. diabetes, tuberculosis, HIV, cardiac diseases, anemia) are factors that predispose to schizophrenia [2].

1.5.3. Dopamine and dopaminergic pathway

Dopamine is a catecholamine neurotransmitter produced by decarboxylation of dihydroxyphenylalanine and is a natural precursor of adrenaline and noradrenaline. [59]. Dopamine receptors (D1 to D5) are distributed in the brain according to the function of certain areas [60]. Dopamine has been associated with motion control, learning, mood, emotion, cognition, and memory [61]. The dysregulation of dopamine pathways is thought to be the cause of various neuropsychiatric disorders [53, 61].

Dopaminergic pathways are routes of neurons whose cell bodies are present in the ventral tegmental area and substantia nigra and that project up to the different synaptic targets [59, 62]. There are four dopaminergic pathways, namely the mesolimbic, mesocortical, nigro-striatal, and tubero-infundibular [59]. The pathways involved in the etiology of schizophrenia are the mesolimbic pathway, starting in the ventral tegmental area in the midbrain and connecting to the limbic system through the nucleus accumbens, cerebellar tonsil, hippocampus, and medial prefrontal cortex, and the mesocortical pathway which projects from the ventral tegmentum to the frontal cortex [59, 63].

Studies have shown that the dopaminergic system is hyperactive responsive in SZP, leading to the exacerbation of psychotic symptoms [64-66]. The dopamine accumulation in the D2 receptors of the nucleus accumbens leads to the positive symptoms. As a consequence, this causes a reduction in dopamine in D2 sites of action (frontal and prefrontal cortex), yielding the negative symptoms [67, 68]. The D1 receptor is one of the major contributors for dopaminergic transmission in the prefrontal cortex. Thus, its dysfunction is implicated in the changes in cognitive behavior and negative symptoms in the disease [61, 69].

1.5.4. Glutamate and glutamatergic pathways

The glutamatergic system is the major excitatory system of the CNS. Glutamate is distributed in most CNS structures and is involved in fundamental cognitive functions such as memory and learning [64]. A type of anesthetic chemically related with the glutamatergic receptor is ketamine, with an affinity larger than N-methyl D-aspartate (NMDA). Intravenous infusion of ketamine in humans induces positive symptoms like delusions, disorganization, visual and auditory hallucinations as well as negative

symptoms like apathy, affective blunting, isolation, and psychomotor retardation, which are similar to symptoms of schizophrenia [64, 70]. However, these symptoms affect more adults than children, suggesting that this mechanism of action is age-dependent [71]. In SZP, there is a reduction of glutamate. Therefore, the hypofunction of NMDA receptors and increased release of glutamate can be a door for treating negatives symptoms [64]. Postmortem studies have identified changes in the density of glutamatergic receptors and their composition in the prefrontal cortex, thalamus, and temporal lobe. A decreased activation of glutamatergic receptors during performance tests in SZP has been observed in these areas [71].

Chronic administration of phencyclidine reduces the dopamine turnover in the frontal cortex and increases the dopamine release in subcortical regions, especially in the nucleus accumbens, demonstrating the link between the glutamatergic and dopaminergic systems [64].

1.6. Antipsychotic treatment

By 1950, the treatment for psychotic patients was their incarceration in nursing homes and hospitals until their death. The discovery of the neuroleptic or major tranquilizer antipsychotics in 1952 marked the beginning of psychopharmacology [2, 11]. Antipsychotics revolutionized the treatment of schizophrenia through an action mechanism based on dopamine D2 receptor antagonism [72, 73]. This discovery allowed the release of psychotic patients to the social living. After administration of chlorpromazine, the patients became neuroleptic, with emotional indifference, without significant reduction of the surveillance [2, 11]. These typical antipsychotic drugs (chlorpromazine was the first one developed) [13] display significant therapeutic effects in positive symptoms [74, 75]. However, they exacerbate negative symptoms [9] and induce significant side effects such as extrapyramidal symptoms [72, 76] hyperprolactinemia, and metabolic alterations [74, 75].

In the 1970s, the discovery of second-generation antipsychotics (e.g. clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) revolutionized the treatment of schizophrenia [13]. A mechanism of action based on lower affinity for D2 receptors and an additional action on serotonin and noradrenaline receptors [9, 68, 77]

allowed the treatment of SZP with fewer extrapyramidal symptoms and beneficial effects on negative symptoms, while maintaining its efficacy for positive symptoms[67, 78, 79]. Nevertheless, it is not clear which mechanism contributes to differences in the action of typical and atypical antipsychotics since both have action on D2 receptors. Clozapine was the first atypical antipsychotic drug approved by the Food and Drug Administration [76] and several studies have proven its efficacy in refractory schizophrenia [79], without blocking nigrostriatal D2 dopamine receptors and resulting in minimal extrapyramidal effects. In addition, 60 % of patients resistant to typical treatment responded to clozapine, regarding not only positive symptoms but also negative ones [13, 80].

Animal models have found that estrogen can reduce dopamine concentration and the sensitivity of dopamine D2 receptors in the brain [42, 46] by increasing serotonin levels in the nucleus accumbens, the same action as atypical antipsychotics [48, 81]. Current research on healthy males and patients suggest that adjuvant estrogen therapy may aid in the treatment of schizophrenia [82].

1.7. Findings in neuroimaging

Magnetic resonance imaging (MRI) is a widely used tool in the clinics as well as in the neurosciences research field. MRI provides very detailed anatomical images of the brain with a strong gray/white matter contrast. It has the advantage of being a non-invasive technique, without the use of any ionizing radiation [22].

There are three main modalities of MRI: structural MRI, which allows us to observe the brain structure; Diffusion Tensor Imaging that allows the study of white matter connectivity using Fractional Anisotropy [83]; and the fMRI that uses the Blood Oxygenation Level Dependent (BOLD) signal to measure changes in the brain activity while the subject is performing a task or while at rest [84, 85].

fMRI is widely used to study cognition, memory, and language. Several studies have evaluated correlates of treatment, providing foundations for understanding the action of antipsychotics in psychiatric patients [86]. However, some aspects of MRI may come as a limitation, especially in the mentally ill [87]. One of the major limitations is claustrophobia and anxiety induced by the introduction of the patient in the scanner tunnel

and the uncomfortable noise caused by the scanner, though this aspect is attenuated by the use of headphones [87, 88].

1.7.1. Structural brain imaging

Structural brain imaging is a technique that allows the determination of the properties of a substance by correlating the energy absorbed against the frequency in the megahertz (MHz) range of the spectromagnetic spectrum [89]. This happens under the influence of a magnetic field and concomitant irradiation of radio waves [89]. In fact, by using MRI, tissues can be characterized using two different relaxation times, T1 and T2. These sequences are a part of the majority of clinical MRI protocols. Pathologies are described in terms of T1 and T2 signal behavior (apart from contrast, anatomical localization and morphology).

The most consistent finding in schizophrenia is the enlargement of the ventricles in elderly patients [90-92]. Another important finding is hippocampal abnormality, including atrophy [93] and change of form. Several researchers proposed that alterations in the hippocampus as a biomarker of schizophrenia [90]. Results of MRI studies in SZP showed that there is a reduction of gray matter in multiple brain areas [11, 94], especially in the right hippocampus [95] and left dorsolateral prefrontal cortex in chronic SZP [94, 96]. Other studies presented strong evidence for atrophy of the gray matter density in the basal ganglia, frontal cortex, cingulum, temporal cortex, bilateral insula, and thalamus [95].

Studies with SZP have shown positive correlations between cognitive deficits and the structure of several brain areas including the amygdala, prefrontal cortex, orbitofrontal cortex, paracingulate cortex, anterior cingulate cortex, temporal parietal junction, and ventral striatum [97]. These areas are involved in social cognition and empathy, which are usually impaired in patients [97].

1.7.2. Functional brain imaging

fMRI commonly performed using the BOLD contrast to detect changes in blood flow in response to neural activity, through local changes in the deoxyhemoglobin concentration in the brain [84, 85]. BOLD imaging takes advantage of inherent differences between oxygenated and deoxygenated hemoglobin [84, 98].

1.7.2.1. Functional connectivity

Functional connectivity is the functional correlation between two regions that can be inferred from common changes in activation over time. Functional connectivity can reflect direct or indirect associations among these regions [88]. Functional connectivity is important to make comparisons of correlations between a region of interest and a seed region [88]. The methods used to address cerebral connectivity are multivariate, namely Principal Component Analysis and Independent Component Analysis [85].

Studies show that patients with schizophrenia have a more diversified, although poorer, connectivity associated with a configuration of complex functional networks less activated [99]. Brain networks of SZP also show a robustness to the electrical attack, which allows for the formation of connective tissue [70, 92]. There is a reduced cluster that forms topographically in the following regions: medial parietal, premotor, right cingulate, and frontal cortices [92]. Others studies found that the dorsolateral prefrontal cortex (DLPFC) is an important area involved in schizophrenia [97, 100]. In addition, there is a dysconnectivity between the hippocampus and dorsolateral prefrontal cortex (HC-DLPFC) during the realization of cognitive tasks (working memory and n-back tasks) in SZP [94, 101, 102]. This is considered an "intermediate phenotype for schizophrenia" and it could be observed in patients, healthy relatives, and carries of two risk polymorphisms [94, 101]. Dysconnectivity is believed to be related to degenerative, developmental, and genetic mechanisms [103].

Studies have shown that patients with schizophrenia have difficulty in recognizing and evaluating the expression of faces [104]. To test the ability to recognize faces, standard images available in the International Affective Picture System (IAPS) are used to stimulate an emotional experience [105, 106]. This instrument consists of a set of images depicting, for example, mutilations, snakes, insects, attack scenes, accidents, contamination, diseases, loss, pollution, dogs, babies, and landscape scenes. The purpose of this tool is to detect the existence of a disconnection between the external emotion of the patient and the real internal feeling, by evaluating the hemodynamic response at the level of the CNS [106]. Studies have shown that healthy subjects, when observing images that portray sad and disagreeable situations, present an increase in the BOLD signal in the thalamus, basal ganglia, mesencephalon, hippocampus, amygdala, medial prefrontal cortex, visual cortex, and cerebellum. However, in SZP, the BOLD signal is reduced in these areas [106]. A recent neuroimaging study showed that, during an emotion induction

task with facial expressions, SZP presented a weaker bilateral amygdala activation [107]. Yet, another study showed reduced activation only in the left amygdala [108].

1.7.2.1.1. Resting-state fMRI

Resting-state fMRI (rs-fMRI) evaluates the spontaneous modifications of the BOLD) [88, 109, 110] while the participant is at rest. The participant must be awake, with eyes closed, in a calm state and try not to think of anything. During the execution of rs-fMRI, several patterns of activated networks can be observed the resting state networks (RSNs)[110]. Among them, the default mode network (DMN), central executive network, and salience network (SN) [111, 112] may be associated with psychopathological and cognitive alterations in psychiatric disorders [113]. One of the most active brain networks during resting-state is the DMN [109, 114]. The DMN is described as a functional network between frontal-parietal regions, including ventromedial regions in prefrontal cortex, posterior cingulate/retrosplenial cortex, and bilateral inferior parietal lobe [110].

Studies showed that the DMN and Salience Network (SN) are altered in schizophrenia [112]. The SN allows the stimulus to initiate a given action [115]. There are few studies addressing the functional connectivity on this network, but they demonstrated a reduction of SN functional connectivity in patients with schizophrenia [112, 116]. Positive symptoms in SZP, such as hallucinations, delusions, disorganization, and psychomotor poverty, may be related to SN deficits [115].

Moreover, the residual symptom burden is more pronounced in patients with lower DMN connectivity [115]. However, it would be very useful to study how DMN networks are altered in patients with paranoid schizophrenia with impairments in empathy. In schizophrenia, there is an aberrant connectivity in the intrinsic organization linked to cognitive processes. This leads to abnormality in coordination and execution of processes in patients with paranoid disease [114]. In theory, the DMN regions are continuously activated, but they can shortly disconnect during an effective cognitive performance task [114]. Some studies indicated that DMN activation might be associated with introspection (internal thoughts, judgments, self-reflections, and conceptions of mental state). Thus, it is important to study this network in neurological and mental disorders, such as schizophrenia [110].

RESEARCH OBJECTIVES

In the present study, we aim to explore the functional brain correlates of the negative symptoms in schizophrenia patients undergoing treatment with different antipsychotics.

The following specific aims were defined:

- To characterize a sample of patients with paranoid schizophrenia and correlate the findings from fMRI with the sociodemographic and clinical factors;
- To evaluate the positive and negative symptoms of schizophrenia and identify the functional brain correlates of cognitive and affective responses using different paradigms with fMRI techniques;
- To compare the functional resting-state networks between SZP and a control group of healthy matched individuals

MATERIAL AND METHODS

3.1. Subjects

Our study included a cohort of 12 male outpatients, diagnosed with paranoid schizophrenia and under treatment for more than 3 months. Patients were selected from the Department of Psychiatry of the *Hospital de Braga*, diagnosed according to DSM V [12] and ICD 10, and 2 psychiatrists confirmed the diagnosis. Given the small sample size of availed sample of patients, we selected only males with a higher disease severity [13, 14, 117].The exclusion criteria were: a history of neurological disease or traumatic brain injury; history of substance abuse or dependence in the past year; a family history of early onset dementia; and patients who did not comply with the medication. Patients were being treated with typical and atypical antipsychotics at the time of scanning (Haloperidol [n = 1], Aripiprazole [n = 3], Olanzapine [n = 2], Paliperidone [n = 2], Clozapine [n = 4], and Quetiapine [n = 1]). All patients underwent clinical and sociodemographic questionnaires. To measure the severity of the disease, clinical symptoms, and psychosocial function we used the PANSS. Before entering the MRI scanner, empathy was evaluated using the IRI.

The control group (n = 6) was selected from the general population. Participants with a history of psychiatric illness, neurological disorders, and family history of schizophrenia were excluded from the study. All patients and control subjects were right-handed, and they underwent a structural MRI to rule out cerebral anatomical abnormalities.

After the procedures had been fully explained to the subjects, participants signed an informed consent, becoming aware of the objectives, methods, possible risks, and guarantee of confidentiality of the data obtained. The research protocol was submitted and approved by the Ethics Committee of the *Hospital de Braga* and the Ethics Committee of University of Minho (SCEVS-UM). (see the Annexes section).

3.2. Material and procedures

Demographic and clinical data were collected using standard questionnaires. Cognitive performance was evaluated with a battery of neuropsychological tests that included Stroop, SRT, Digits Symbol Substitution Test (DSST) and Digits Spam. To characterize patients' symptoms, PANSS was used. Three dimensions were obtained from this scale:

positive, negative, and general. IRI was applied to measure empathy and four dimensions were obtained: perspective taking, empathic concern, personal anguish, and fantasy. All neuropsychological and clinical tests were applied prior to scanning and took approximately 45 minutes.

Task-based fMRI and resting-state fMRI were used to obtain the brain activation profile of the subjects. This profile was later correlated with the scores obtained in IRI, PANSS, and cognitive tests. All the paradigms were applied during scanning lasting around 1 hour. In the next sections, we present the details for PANSS, IRI, and neuropsychological tests, and MRI acquisition.

3.3. Data collection

3.3.1. Sociodemographic and clinical questionnaire

Sociodemographic information was collected to access individual's personal data and lifestyle, namely: age and disease onset age, marital status, residence, occupation, years of formal education, smoking habits, family composition, and familiary and social support.

The participants were also enquired about clinical data such as intake of medication to treat psychiatric disorders, psychiatric medical history, smoking habits, alcohol consumption, use of drugs, previous suicide attempts, and other comorbidities. We also collected schizophrenia-related information such as family history, evolution of the disease, age of the first episode, and number of crises suffered.

3.3.2. Neuropsychological tests

Neuropsychological assessment tests allow us to diagnose and generally classify brain damage, brain disease, and brain mental disorder [119]. With neuropsychological tests, we can make diagnoses, differential diagnoses, prediction of functional potential, measurement of response to treatment, and clinical correlation with imaging findings. It is possible to determine psychological functions such as attention, short or long-term memory, degree of distraction and concentration, language expression and communication, cognition (learning ability, logical and abstract reasoning, organization

and visual coordination and planning, synthesis and organization capacity) [119]. In this study, all the SZP underwent psychological evaluation tests.

3.3.2.1. PANSS

The PANSS is a well validated psychometric instrument widely used in the study of schizophrenia [118, 119]. The scale was validated in the Portuguese population and features 30 items divided into 3 categories: a positive scale with 7 items, a negative scale with 7 items, and a general scale with 16 items. Each item is rated on a Likert scale ranging from 1 (absent) to 7 (very severe) [118] allowing the following classification:

Symptomatology type:

- Positive (3 or more symptoms with a score ≥ 4 in the positive range and less than 3 symptoms with a score ≥ 4 in the negative range);
- Negative (3 or more symptoms with a score ≥4 in the negative range of 3 symptoms with a score ≥ 4 on the positive range);
- Mixed (3 or more symptoms with a score ≥ 4 in both ranges);
- No kind (if the above criteria do not apply)

3.3.2.2. IRI

IRI is an instrument used to measure empathy [29]. The version validated for the Portuguese population comprises 24 items (seventeen positive, seven negative), forming four subscales with six items each: Subscale perspective Taking (2, 7, 9, 17, 21, 24) that measures the perspective of others. Subscales of empathic concern (1, 3, 8, 12, 16, and 18) that measures the tendency to feel warmth and compassion for others. Subscale of personal anguish (5, 11, 14, 15, 20, and 23) that evaluates the discomfort caused by the observation of the negative experiences of others. Subscale of fantasy (IRI_FS: 4, 6, 10, 13, 19, 22), which evaluates the tendency to identify with the character fictitious [24].

For each IRI's item, the subject is asked to indicate how well the situation describes him, and according to the five-point Likert scale, which ranges from 0 (not describe) to 4 (describes very well). In inverted items, the count is reversed. The score of each subscale is the mean of answers of that subscale.

3.3.2.3. STROOP

The STROOP test is a measure of cognitive control/flexibility and assesses the subject's ability to keep a goal in mind and suppress a common familiar response in favor of a less familiar [117]

In this study, we used the Portuguese version of the Stroop Test of Colors and Words. This version consists of a data record sheet, test quotation, instruction sheet and three response slides, each containing 100 items distributed in five columns of 20 elements. In the first slide, the words "GREEN", "RED", and "BLUE" are printed in black ink and arranged in a random way. In the second slide, there are 100 equal elements - "XXXX" - printed in green, red, and blue, also in a random order. There is no correspondence between the colors of the first blade and the order of the colors of the second blade. Finally, in the third slide, the words of the first page are printed in the color of the second, with an incongruent correspondence between the color of the ink and the meaning of the word. The results sheet and test quotation have different fields that allow counting the number of words read on the first slide, the number of colors read on the second slide and the number of named colors (PC) of the printed words [117].

The results are obtained by counting the number of words read on the first slide and the colors listed on the second and third slides over a period of 45 seconds. Performance is measured by the time taken during the test and best results correspond to shorter holding times [117].

3.3.2.4. Digit Symbol Substitution Test

The Wechsler Digit Symbol Coding Tasks test is indicated to measure executive function (processing speed, associative memory, and graph motor speed). Using a given key of numbers associated with symbols, participants should correctly substitute the symbols for the numbers, during a certain stipulated time interval. In this study, we used 2 minutes. The number of correctly replaced symbols is then evaluated operationally.

3.3.2.5. Digits Spam

Digit Spam is composed of a sequence of numbers to evaluate the index of working memory. It is subdivided into 2 subtypes: (1) first, direct order – consisting of 16 series of direct-order digits, with a gradual increase in the number of digits in each series. The participant must repeat each series; (2) second, reverse order – the test consists of 14 series of digits, also with a gradual increase in the number of digits in each series. The

participant has to repeat the digits in reverse order. The direct order is applied first, followed by the inverse, which is administered independently if the examinee fails completely in the direct order. Each item is formed by 2 sets of digits and the test ends when the participant fails the 2 sets of digits that compose 1 item. The maximum score in the subtest is 30 points. The purpose of this test is to study working memory, attention, encoding, and auditory processing.

3.3.2.6. SRT

The SRT is a selective memory neuropsychological test that was adapted for the Portuguese population [118, 119]. It aims to evaluate verbal learning and long-term memory [120]. The test consists of a list of 12 unrelated words. Immediately after the examiner read all the words, the participant is granted a period of 2 minutes to remember as many words as possible, no matter the order [118]. After this first trial, the examiner repeats the non-recalled words and, then, the participant is granted a period of 2 minutes to repeated the 12 words again. Six attempts to remember the 12 worlds are made. The participant is asked to verbally repeat the words 30 minutes after the last test of selective reminders [118]. In this study, we selected: (a) the total of immediately recalled words across trials (SRT Total Immediate Recall [IR]), (b) the total of words recalled after the 30-min interval (SRT Total Delayed Recall [DR]), (c) the long-term storage (LTS, words recalled twice in a row, assumed to be in long-term/permanent storage from that point on), (d) the short-term storage (STS, the remaining words not in LTS) [118], and (e) The Consistent Long-Term Retrieval, (CLTR, remembered words in subsequent trial) [121]

3.4. MRI data acquisition

The imaging session was performed at Hospital de Braga on a clinical approved Siemens Magnetom Avanto 1.5 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) and using a 12-channel receive-only head-coil. For the resting state fMRI acquisition, a BOLD sensitive echo-planar imaging sequence was used: 30 axial slices, repetition time (TR) /echo time (TE) = 2,0 s/30 ms, Flip Angle (FA) = 90°, slice thickness = 3.5 mm, slice gap = 0.48 mm, voxel size = 3.5 × 3.5 mm2, FoV (Field Of View) = 224 x 224 mm^2 and 180 volumes. During the resting state acquisitions, participants were instructed to remain calm and still, keep their eyes closed and think about nothing in particular. For the task

based fMRI we used a similar sequence with the following parameters: 38 axial slices, TR/TE = 2,5 s/30 ms, FA = 90°, slice thickness = 5 mm, slice gap = 0.48 mm, voxel size = 3.5 × 3.5 mm2, Flip Angle (FoV) = 256 x 256 mm^2 and 314 volumes. Two sequences were acquired per participant (run 1 and 2).

One high-resolution T1-weighted Magnetization-Prepared Rapid Acquisition with Gradient Echo sequence (MPRAGE), with 1 × 1 × 1 mm^3 voxel size, TR 2.73 s, TE 3.48 ms, FA 7°, X (FoV) 234 × 234 mm^2, and 176 slices was acquired. This anatomical sequence was used to project the functional/statistical maps. All anatomical images were evaluated to exclude clinical alterations.

3.4.1. Resting-state – functional magnetic resonance data preprocessing

Resting-state fMRI data preprocessing was performed using the FMRIB Software Library tools (FSL v5.07, http://fsl.fmrib.ox.ac.uk/fsl/). The first 5 volumes of each functional time series were discarded to assure signal stabilization. The remaining images were corrected for the acquisition delay between slices (slice timing) and for head motion. Each subject's functional data set was then normalized to the Montreal Neurological Institute (MNI) standard space through an indirect procedure that included: (i) skull stripping of the mean image of the functional acquisition; (ii) rigid-body registration of the mean functional image to the skull stripped structural scan; (iii) affine registration of the structural scan to the MNI T1 template; (iv) nonlinear registration of the structural scan to the MNI T1 template using the affine transformation previously estimated as the initial alignment; (v) nonlinear transformation of the functional acquisition to MNI standard space through the sequential application of the rigid-body transformation and the nonlinear warp followed by resampling to 2 mm isotropic voxel size. Linear regression of motion parameters, mean white matter (WM) and cerebrospinal fluid (CSF) signal and motion outliers was performed and the residuals of the regression were band-pass temporal filtered (0.01–0.08 Hz) and used for the subsequent analysis.

Next, a Probabilistic Independent Component Analysis was performed with Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC), distributed with FSL. ICA is a data driven analysis that isolates components or non-overlapping spatial maps corresponding to regions evidencing coherent time-courses. The software estimates group-wise spatial maps that correspond mainly to Resting State Networks (RSNs). The software automatically estimated the number of

independent components. To study subject-specific components, a dual regression was used. In this regression, confounding factors, namely motion parameters (rotation and translation estimates), motion outliers, and mean WM and CSF signals were included.

number of independent components. In order to study subject-specific components, a dual regression was used. In this regression, confounding factors, namely motion parameters (rotation and translation estimates), motion outliers and mean WM and CSF signals were included.

RSNs of interest were identified by visual inspection in combination with spatial correlations between the obtained RSNs and RSNs templates available from a public data set from the Functional Imaging in Neuropsychiatric Disorders (FIND) Lab at Stanford University.

3.4.2. IAPS

The stimulus was block-designed using E-Prime 3.0 (Psychology Software Tools, Inc., USA) and was presented through a mirror on a screen.

IAPS provides a set of normatively rated emotional stimuli for investigation of emotion and attention. Stimuli are composed of color photographs within a wide range of semantic categories. The variance in emotional assessments has two main dimensions: the valence (ranging from pleasant to unpleasant) and the arousal (ranging from calm to excited) [105, 122]

In our study, we selected pictures with different valence scores from the IAPS database: negative (< 2.5), neutral (2.5 to 5), and positive (> 5) [123]. The IAPS stimulus was designed differently for male and female participants, but the pictures valence was matched between genders. Thirty-six negative, 36 neutral, and 36 positive pictures were randomly presented to the participants per run. Two runs were acquired with 108 pictures. In the first run, a text cue matching the picture valence was shown before the picture presentation (‘Negative’, ‘Neutral’, or ‘Positive’) – congruent cue. In the second run, a meaningless text cue was shown before the picture (‘dghntfu’) – incongruous cue. The different cues allowed the modulation of the picture anticipation effect. The pictures sequence in the first and second run was different to avoid habituation effects but the pictures were matched for valence. Each stimulation block consisted of a cue with 0.5 s, followed by a baseline image with 3 s (black screen with a white fixation cross), and lastly

the IAPS picture with 2 s. random interstimulus intervals (ITI) were defined between blocks with 1.6 to 3 s (Figure 2). To avoid attentional losses during stimulation, we required the participants to press a button whenever a picture was displayed on the screen[123].

After fMRI, the participants evaluated the pictures outside the scanner, using a scale ranging from 1 (highly dislike) to 9 (highly like).

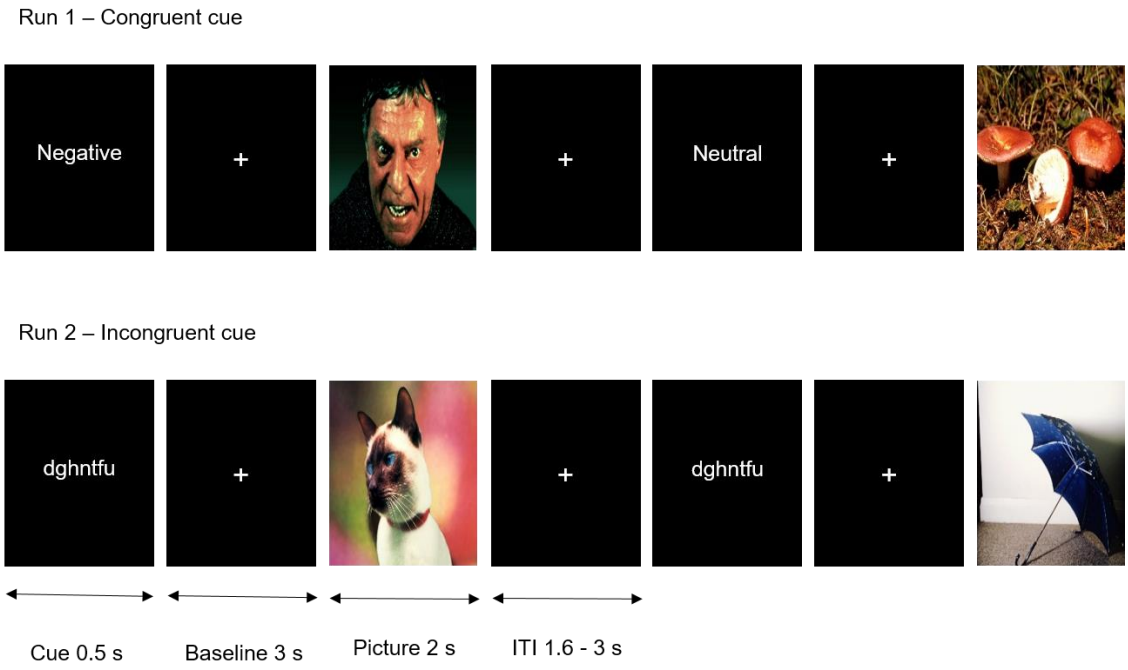

Figure 1 – Part of the stimulus sequence presented to the participants inside the magnetic resonance imaging scanner (2 blocks). Negative, neutral, and positive pictures from the International Affective Picture System database were randomly presented. ITI = Interstimulus intervals.

3.4.2.1. IAPS data processing

Brain imaging analysis was carried out using Statistical Parametric Mapping (SPM) version 12 (The FIL Methods group, U.K.) running in Matlab version R2016a (The Math Works, Inc., U.S.A.).

SPM uses a General Linear Model (GLM) to measure voxel-based differences in the magnitude of the BOLD) signal elicited by a specific task. The fMRI signal is modeled as a linear combination of explanatory functions (predictors) and a residual error [126].

Preprocessing steps on fMRI data are applied to meet the GLM assumptions (normal distribution and error term independence) and enhance statistical power. Physiological (cardiac and respiratory processes) and no physiological noise (instrumental and head movement) affect the fMRI images [126]. Images were firstly corrected for slice-timing (second slice as reference). Head motion correction was applied by realigning images to the average sequence image (six-parameter rigid-body spatial transformation). Images were spatially transformed to the standard MNI) space and then resampled to a 2 x 2 x 2 mm3 resolution. Spatial smoothing (8 mm Full-Width Half-Maximum Gaussian kernel) and high pass temporal filtering (width 128s) were lastly applied [127, 128].

After preprocessing, individual first-level analyses were performed for run 1 and 2 together. Five GLM predictors were defined: negative pictures, neutral pictures, positive pictures, congruent cue, and incongruous cue. The six predictors resulting from motion correction were also added to GLM to account for the head movement effect. The intervals between pictures and cues were assumed as a baseline. Four contrasts were defined based on paired-samples t-test: negative versus neutral pictures, positive versus neutral pictures, positive versus negative pictures, and negative versus positive pictures.

Group second-level analysis was performed with two-way repeated measures analysis of variance (ANOVA) for each contrast defined during first-level analysis [129].

If no cluster survived FWER correction, clusters with p-values under 0.001 and a minimum size of 50 voxels were considered statistically significant.

3.5. Statistical Analysis

Data from participants' characterization, neuropsychological, and cognitive assessment are presented in mean and standard deviation (SD) and in absolute frequency (n) and relative frequency (%). Independent samples t-test was used to test differences between patients and controls. Pearson coefficient was used to assess the correlation between psychological and cognitive variables. Statistical analysis was conducted using the SPSS package v24 and statistical significance was defined at $p < 0.05$ level.

The statistical analysis of the functional data was performed using SPM12 (Statistical Parametrical Mapping, Wellcome Trust Centre for Neuroimaging, UK). The within-group analysis was done using one-sample t-test and the between-group analysis using a two-sample t-test. The results were considered significant for a p value below 0.001, corrected for multiple comparisons using a combination of an uncorrected height threshold of $p < 0.001$ with a minimum cluster size. Anatomical labeling was performed using the Anatomical Automatic Labeling atlas (AAL) [130].

RESULTS

4.1. Socio-demographic characterization

Table 1 presents the socio-demographic characterization of patients and controls. The sample consists of 12 male outpatients with age 43 ± 10 years (mean ± SD) and years of formal education 12 ± 5 years. The first psychotic episode occurred at the age 23 ± 9 years, with the majority of patients (58.3 %) having their episode in early adulthood. The illness duration was 19 ± 10 years. The control participants had a tendency fora higher educational status (SZP 12 ± 5 years, controls 15 ± 6 years). There were no significant group differences in demographic features such as age (t (16) = 0.232, $p = 0.819$) or years of educations (t (16) = -0.673, $p = 0.511$).

Table 1 – Socio-demographic characterization of schizophrenic patients and healthy controls.

	Patients (n = 12)	**Healthy controls (n = 6)**	***p* value**
Sociodemographic characterization – M; SD			
Age (years)	43; 10	41; 14	0.819
Education (years)	12; 5	15; 6	0.511
Occupation - n (%)			
Unemployed	3 (33.3%)		
Retired	6 (50.0%)		
Inability	1 (8.3%)		
Other	1 (8.3%)		
Illness characterization– M; SD			
Age of first psychotic episode	23; 8.7	---	---
Age class – n (%)			
Young	7 (58.3%)	---	---
Young adult	2 (16.7%)	---	---
Adult	3 (25.5%)	---	---
Illness duration	19 ;10	---	---
Number of hospitalizations	5; 5	---	---

M = Mean; SD = Standard deviation.

The mean score for PANSS was 55 (SD = 12). The mean values of the subscales were positive: 16 ± 7, negative 12 ± 4, and general 28 ±7 (Table 2).

Empathy, measured by IRI, presented a mean total score of 49 (SD = 12) and the four subscales presented the following mean scores: perspective taking – 15 ± 4, empathic concern 13 ± 4, personal anguish 10 ± 6, and fantasy 10 ± 5 (Table 2).

Table 2 – Neuropsychological characterization of schizophrenic patients.

	Patients (n=12) M, SD
PANSS	
Total score	55.0
Negative	12.4
Positive	16.7
General	28.7
IRI	
Total score	49.0
Perspective Taking	15.4
Empathic concern	13.4
Personal anguish	10.6
Fantasy	10.5

PANSS = Positive and Negative Syndrome Scale; IRI = Interpersonal Reactivity Index; M = Mean; SD = Standard deviation.

4.2. Correlation between PANSS total and IRI

As displayed in Table 3, PANSS total score was positively correlated with PANSS negative (r = 0.691) and general (r = 0.812) scores. This means that the variance of PANSS total score is significantly explained by PANSS negative and general scores. The negative PANSS had a negative correlation (r = -0.661) with the empathic concern subscale of IRI, indicating that the higher the negative symptoms in these patients the less they care about the suffering of others. PANSS total score presented a negative correlation (r = -0.649) with empathic concern, indicating that the higher the PANSS total score the lower the patients' ability to feel compassion for others.

IRI total score was significantly correlated with IRI fantasy subscale (r = 0.901), which means that the highest score on the IRI scale was strongly related to patients' ability to engage with others' situations. The IRI subscales perspective taking and emphatic concerns were positively correlated (r = 0.883), indicating that the more the patient tends to put himself in others' place, the more he feels sorry for the other. There was a positive correlation between perspective taking and empathic concern (r = 0.830), meaning that the greater the patient's ability to look on both sides of a situation the greater the ability of the patient to feel compassion for others.

There was a positive correlation between total IRI (r = 0.667) and backward digits. This result means that the highest score on the IRI scale is related to a higher working memory capacity (Table 4).

Table 3 – Correlation of the neuropsychological tests.

	Negative	General	Total	Perspective taking	Empathic concern	Personal discomfort	Fantasy	Total
PANSS								
Positive	0.018	0.281	0.473	-0.256	-0.231	0.483	0.376	0.217
Negative		0.242	**0.691***	-0.561	**-0.661***	-0.007	-0.472	-0.574
General			**0.812****	-0.038	-0.373	0.144	-0.193	-0.145
Total				-0.402	**-0.649***	0.225	-0.260	-0.333
IRI								
Perspective taking					**0.830****	-0.314	0.388	**0.577***
Empathic concern						-0.161	0.519	**0.707***
Personal discomfort							0.501	0.515
Fantasy								**0.909****

PANSS = Positive and Negative Syndrome Scale; IRI = Interpersonal Reactivity Index

Table 4 – Correlation between Positive and Negative Syndrome Scale and cognitive tests.

	SRT			STROOP			Digits			DSST
	LTS	CLTR	DR	Words	Colors	W&C	Forward	Backward	Total	Total
PANSS										
Positive	0.071	0.021	0.014	0.184	0.305	0.400	0.237	0.342	0.293	-0.249
Negative	0.346	0.222	0.242	0.031	0.136	0.058	0.330	-0.389	0.372	-0.156
General	0.319	0.313	0.412	0.210	0.456	0.173	0.160	0.160	0.013	-0.161
Total	0.017	0.073	0.119	0.175	0.321	0.207	0.204	-0.014	0.107	-0.255
IRI										
Perspective taking	0.198	0.211	0.171	0.228	0.193	0.056	0.090	0.374	0.235	0.070
Empathic concern	0.028	0.016	0.238	0.189	0.162	-0.213	0.026	0.277	0.143	-0.019
Personal discomfort	0.348	0.437	0.174	0.085	-0.189	-0.029	0.188	0.565	0.414	0.260
Fantasy	0.276	0.384	0.012	0.108	-0.091	-0.197	0.187	0.516	0.361	0.077
Total	0.318	0.420	0.055	0.213	-0.014	-0.179	0.195	**0.667***	0.450	0.166

PANSS = Positive and Negative Syndrome Scale; IRI = Interpersonal Reactivity Index; SRT = Selective Reminding Test; LTS = Long-term Storage; CLTR = Consistent Long-term Retrieval; DR = Delayed Recall; W&C = Words and Colors; DSST = Digital Symbol Substitution Test.

4.2.1. Affective ratings

For the IAPS stimulus, we performed a one-sample *t*-test using all contrasts described in the Material and procedures section. We found significantly greater activation in the left temporal lobe and superior temporal gyrus, and the right temporal lobe and middle temporal gyrus, when viewing positive images in relation to the display of neutral images in the SZP (Figure 2).

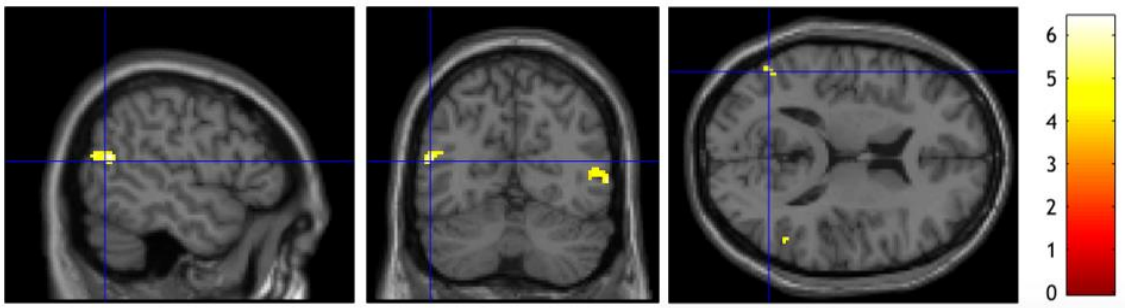

Figure 2 – Activated voxels for the contrast positive > neutral. The image represents the brain in the neurological convention.

4.2.1.1. Correlation of IAPS with the total IRI scale

When we correlated the response to the IAPS stimulus with the total score in the IRI scale we observed that: (1) negative pictures compared to neutral were associated with an increased activation in the Postcentral Left gyrus (PCL), Occipital Lobe in the region of Lingual Right cuneus, Frontal Lobe (FL) in the region of Precentral Gyrus Left (LPCG) and Precentral Gyrus Right (RPCG), Parietal lobe(PL) in the region of Left inferior Parietal (LIP) and precuneus, and left Temporal Lobe (TL) in the region of temporal superior gyrus Left (LTSG). In addition, there was a positive correlation between the contrast negative > neutral with the total IRI scale (Figure 3a). A positive correlation was observed between total IRI and this contrast, associated with the activation in the right cerebellum posterior lobe (Figure 3b). There was a negative correlation between the contrast positive > negative and the total IRI, associated with the activation in the right middle frontal gyrus, whereas the correlation was positive between the contrast negative > positive and the total IRI for the same region (Figure 3c)

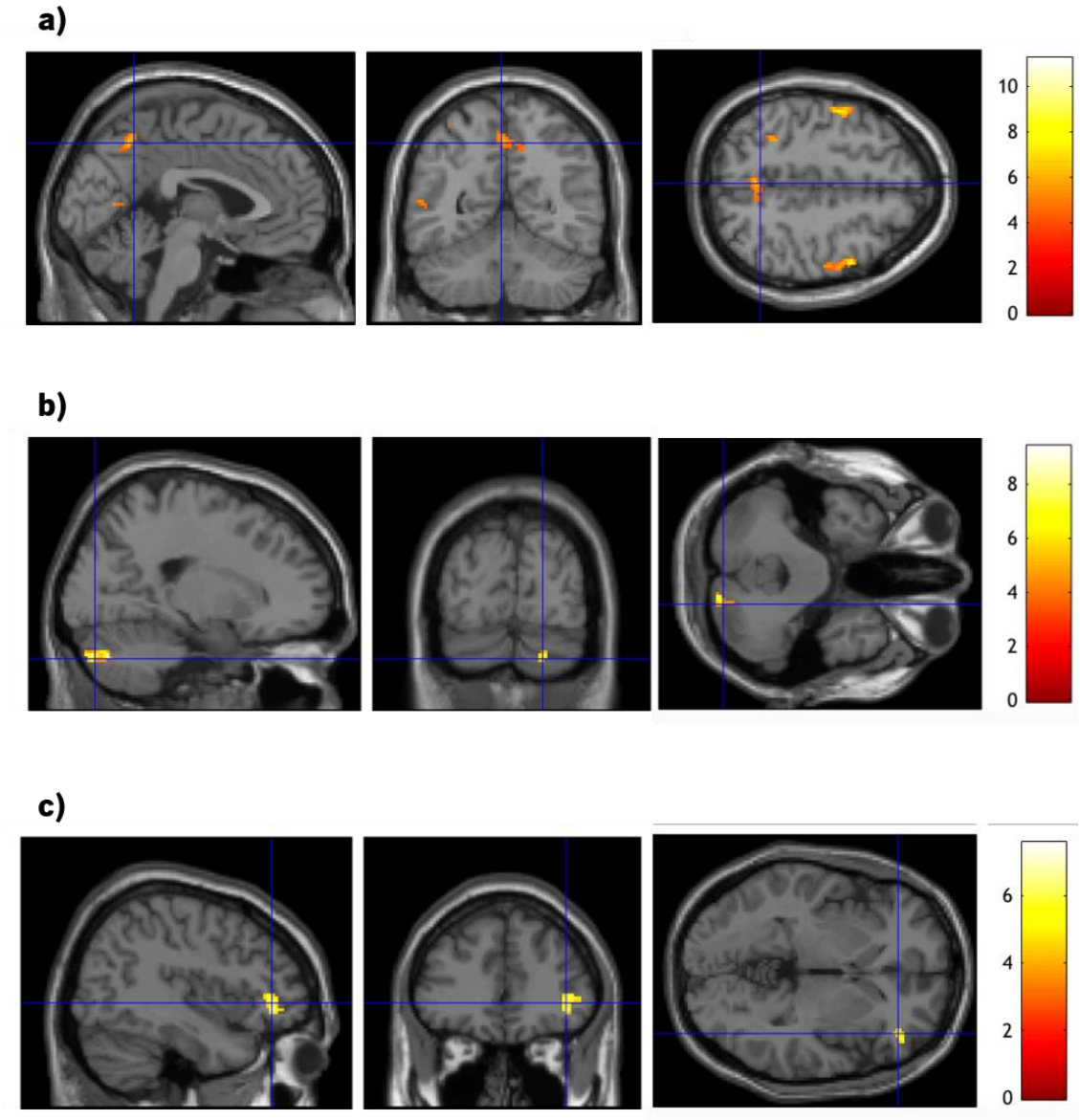

Figure 3 – Activated voxels regarding correlations between the a) contrast negative > positive and Interpersonal Reactivity Index, b) positive > negative and Interpersonal Reactivity Index, and c) negative>positive and Interpersonal Reactivity Index.

4.2.1.2. Correlations between IAPS paradigm with the subscale of IRI

We deepened the analysis to know which of the dimensions of the IRI scale was contributing more to the results observed. We analyzed the effects of the correlations of the IAPS images with perspective taking, empathic concern, personal anguish, and fantasy subscales. We found that: (1) negative > neutral presented a positive correlation with the personal discomfort dimension associated with the activation of the clusters in the regions Frontal lobe - Middle Frontal gyrus - precentral Right, Parietal lobe - superior

parietal lobule Left, Frontal lobe - Precentral Gyrus Right. This means that the more difficulties the patient has to express discomfort in relation to the distressing situations of others the greater the activation of the clusters in these areas (Figure 4a); (2) In contrast, the positive > neutral and the dimension taken from perspective presented a negative correlation associated with the activation in the Limbic Lobe (LL) – Para hippocampal Gyrus Right, Limbic Lobe – Para hippocampal Gyrus Fusiform Right, Temporal lobe (TL) - Sub-gyral - Occipital sup Right (Figure 4b); (3) When we used the contrast negative > positive, the same regions mentioned above showed a positive correlation with the subscale taken from perspective, which means that the more difficult the patients have to perceive that a situation has two sides, the greater the activation of the clusters in these areas; (4) In the other dimensions, no significant results were found.

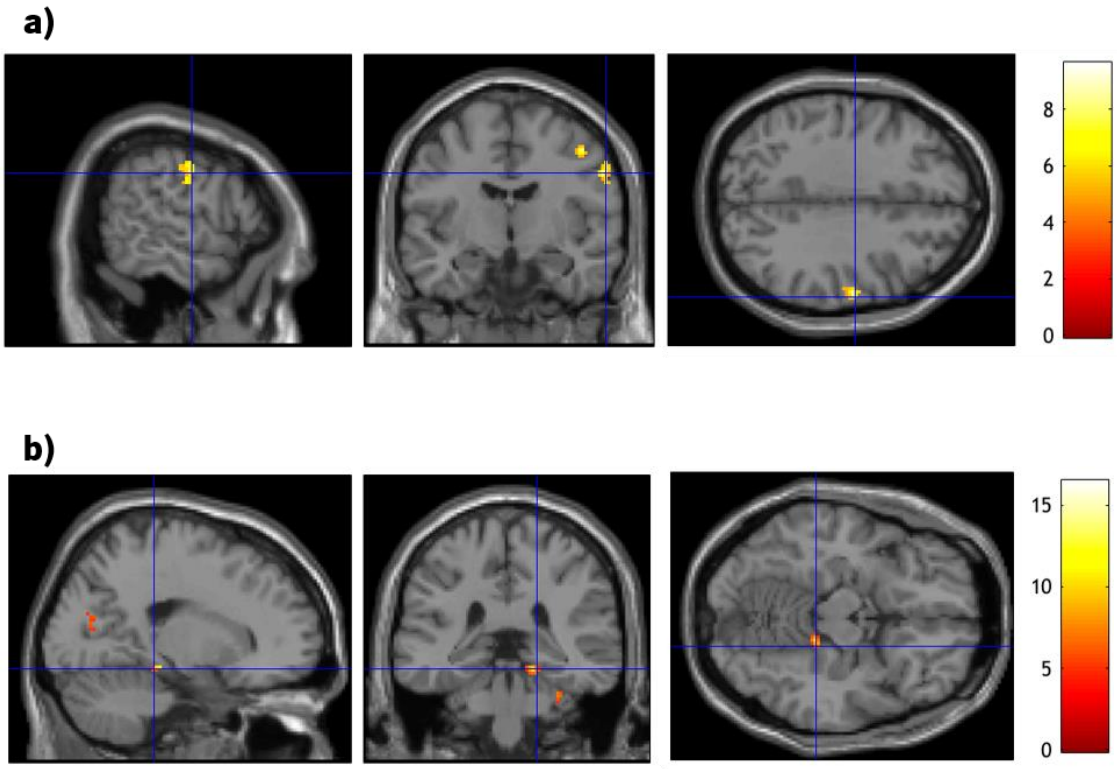

Figure 4 – Correlations between Interpersonal Reactivity Index subscale with the International Affective Picture System paradigms: personal discomfort with a) contrast negative > neutral, and b) contrast positive>neutral.

4.3. Correlation with clinical variables

4.3.1. PANSS subscales and IAPS dimensions:

The table below (Table 6) summarizes the correlations between the contrast negative > neutral, negative > positive, and positive > negative and PANSS negative, positive, and general, respectively. The results of each correlation were: (1) negative > neutral - the negative inducing pictures compared to neutral were associated with an increase of activation in the Cerebellum Anterior Lobe Left (LCAL), Parietal Lobe - Postcentral Gyrus Right (PL-RPCG), Sub-lobar - Insula Right, and right Cerebellum Posterior Lobe (RCPL) (Figure 5a). Moreover, the correlation with negative PANSS was negative; (2) negative > positive - the activated voxels in this contrast occurred in Frontal Lobe - Precentral Gyrus Left (FL-LPCG) in the negative inducing pictures compared to positive, and the correlation with positive PANSS subscale was positive. When we changed the contrast to positive > negative, the correlation became negative (Figure 5b); (3) In relation to the general subscale, we noticed a negative correlation with all the contrasts of the IAPS paradigm in the Sub lobar region - Insula Right (Figure 5c).

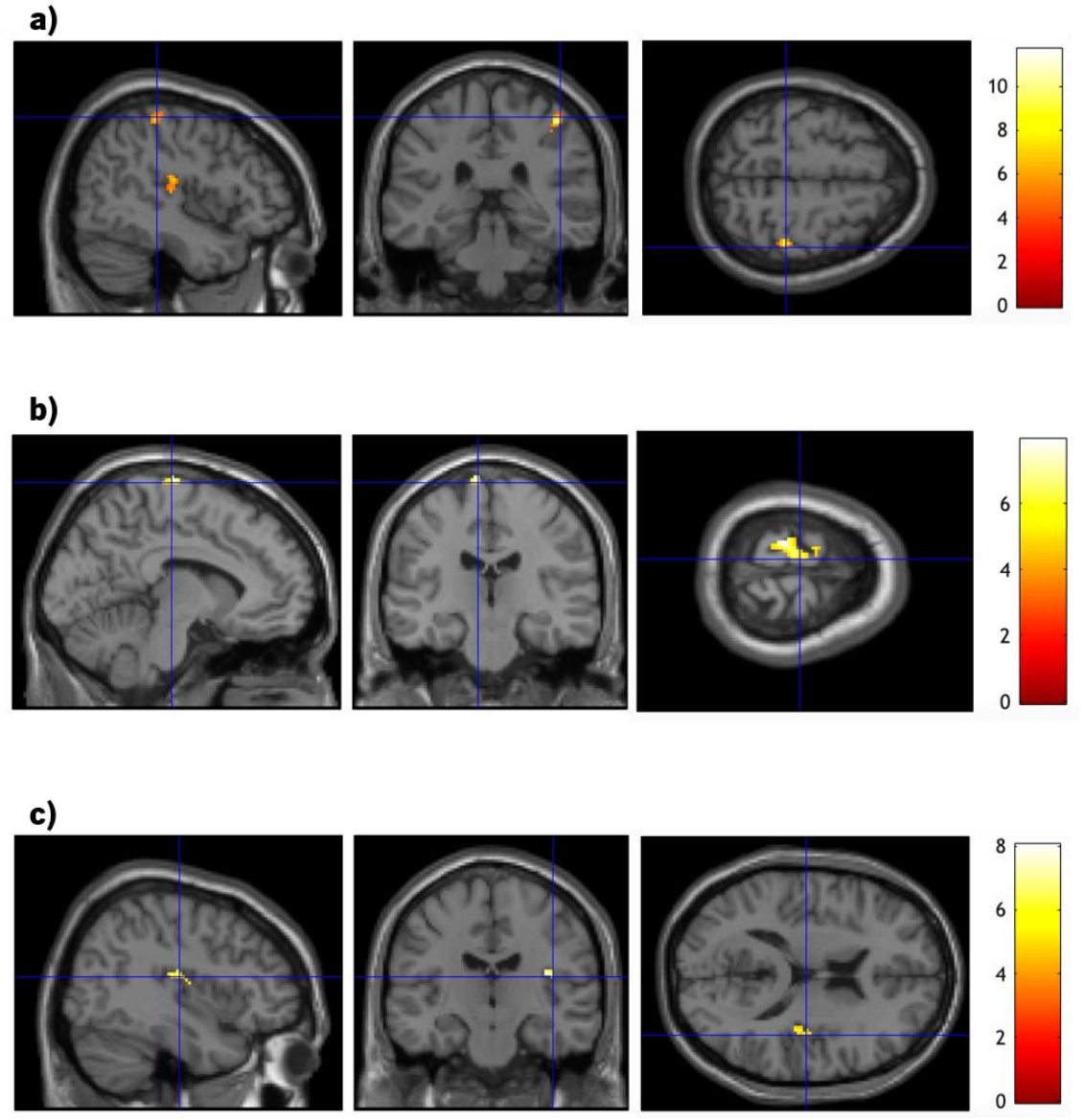

Figure 5 – Correlations between Positive and Negative Syndrome Scale subscale with International Affective Picture System paradigm: a) Positive and Negative Syndrome Scale-negative with positive > negative contrast, b) Positive and Negative Syndrome Scale positive with contrast positive > negative and c) Positive and Negative Syndrome Scale general with all the contrast of International Affective Picture System, are the ones that we found.

Table 5 – Results of correlates of brain regions activity in schizophrenic patients during the International Affective Picture System paradigm and correlations with the Interpersonal Reactivity Index and Positive and Negative Syndrome Scale.

	Brain regions	Side	Coordinates (mm)[a] x	y	z	Zmax score[b]	Voxels
Positive > Neutral	**Temporal lobe**						
	Superior Temporal Gyrus	Left	-52	-60	18	4.06	81
	Middle Temporal Gyrus	Right	58	-64	2	3.7	76
Correlation of IAPS vs total IRI							
Negative > Neutral, positive correlation *vs* total IRI	Postcentral	Left	-34	-42	68	5.01	85
	Occipital Lobe						
	Lingual - cuneus	Right	6	-66	4	4.47	89
	Frontal Lobe						
	Precentral Gyrus	Left	-52	-4	50	4.35	65
	Precentral Gyrus	Right	-48	-40	54	4.31	97
	Parietal lobe						
	Parietal Inferior	Left	52	6	48	4.18	99
	Temporal Lobe						
	Superior temporal gyrus	Left	-56	-48	10	4.13	60
	Parietal Lobe						
	Precuneus	Left	-2	-58	48	3.98	92
Positive > Neutral, positive correlation *vs* total IRI	**Cerebellum posterior lobe**	Right	20	-74	-34	4.97	104
Positive > Negative, negative correlation *vs* total IRI	Middle Frontal gyrus	Right	42	38	-6	4.41	115
Negative > Positive, positive correlation *vs* total IRI	Middle Frontal gyrus	Right	42	38	-6	4.41	115
Correlation of IAPS vs IRI subscales							
Negative > Neutral, positive correlation *vs* personal discomfort	**Frontal lobe** Middle frontal gyrus precentral	Right	50	-2	46	4.19	55
	Parietal lobe Superior parietal lobule	Left	-30	-54	62	4.16	59
	Frontal lobe Precentral Gyrus	Right	60	-10	36	3.96	65
Positive > Negative, negative correlation vs perspective taking	**Limbic Lobe** Parahippocampal Gyrus	Right	18	-32	-12	4.95	41
	Limbic Lobe Parahippocampal Gyrus Fusiform	Right	32	-30	-28	4.46	35
	Temporal lobe Sub-gyral – Occipital_sup	Right	26	-78	20	4.32	36
Negative > Positive, positive correlation *vs* perspective taking	**Limbic Lobe** Parahippocampal Gyrus	Right	18	-32	-12	4.95	41
	Limbic Lobe Parahippocampal Gyrus Fusiform	Right	32	-30	-28	4.46	35
	Temporal lobe Sub-gyral – Occipital_sup	Right	26	-78	20	4.32	36
Correlation of IAPS vs total PANSS							
Positive > Negative, negative correlation *vs* total PANSS	Fusiform	Right	38	-38	-26	4.42	63
	Temporal Lobe Middle temporal gyrus		54	-8	-20	3.8	66
Negative > Positive, positive correlation *vs* total PANSS	Fusiform	Right	38	-38	-26	4.42	63
	Temporal Lobe Middle temporal gyrus		54	-8	-20	3.8	66
Correlation of IAPS vs PANSS subscale							
Positive > Neutral, negative correlation *vs* negative PANSS	Cerebellum Anterior Lobe	Left	-18	-50	-18	4.7	50
	Parietal Lobe Postcentral Gyrus	Right	44	-32	56	4.69	50
	Sub-lobar Insula	Right	48	-22	22	4,1	52
	Cerebellum Posterior Lobe	Right	16	-70	-22	3.86	70
Negative > Positive, positive correlation *vs* positive PANSS	**Frontal Lobe** Precentral Gyrus	Left	-10	-20	80	4,07	114
Positive > Negative, negative correlation *vs* positive PANSS	**Frontal Lobe** Precentral Gyrus	Left	-10	-20	80	4.07	114
Negative > Positive, negative correlation *vs* general PANSS	Sub-lobar Insula	Right	42	-10	12	4.1	50
Positive > negative, positive correlation *vs* general PANSS	Sub-lobar Insula	Right	42	-10	12	4.1	50

[a]Montreal Neurologic Institute coordinates in the local point maximal activation included in the cluster; [b]Activation differences were considered significant at height threshold (p<0.001) and extent threshold of a minimum cluster size; PANSS = Positive and Negative Syndrome Scale; IRI = Interpersonal Reactivity Index; IAPS = International Affective Picture System.

4.4. Resting state network

4.4.1. Component selection and visualization

Using SPM, we performed the one sample *t*-test, where we identified 8 resting-state networks. Figure 6 shows dorsal and ventral DMN, left and right Executive Control Network (ECN), sensorimotor and primary visual, visuospatial and precuneus. The location of selected foci of activation and the corresponding *z*-scores are summarized in Table 7.

Independent two-sample t-test was performed to compare groups (SZP and healthy control), but no significant differences were observed.

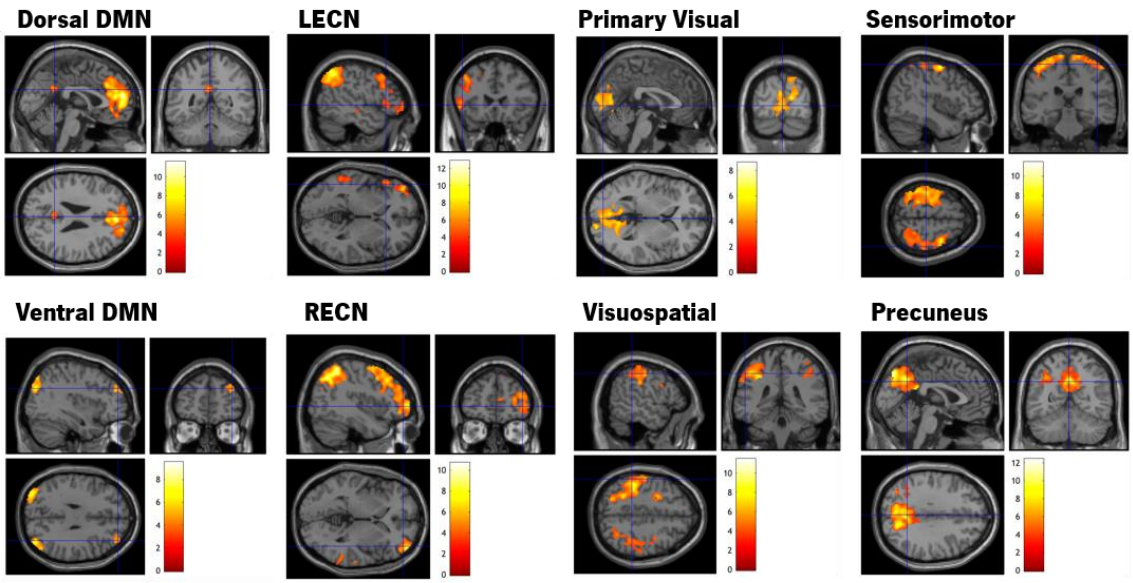

Figure 6 – Reference maps network identified by multiscale individual component clustering analysis of resting-state data. DMN = Default Mode Network; LECN = Left Executive Control Network; RECN = Right Executive Control Network.

Table 6 – Foci of activation in resting-state networks of seven components of interest. Selected clusters are significant at cluster level corrected with a family-wise error threshold of $p < 0.001$.

	Brain regions	Side	Coordinates (mm)[a]			Zmax score[b]	Voxels
			x	y	z		
Dorsal DMN	**Frontal lobe**						
	Medial Frontal Gyrus	Right	6	46	26	6.03	4916
	Limbic Lobe						
	Cingulate Gyrus	Left	-2	-50	28	4.27	114
Ventral DMN	**Parietal lobe**						
	Precuneus	Left	-40	-82	36	5.52	488
	Superior Parietal Lobule	Right	30	-70	50	5.45	3841
	Frontal lobe						
	Middle Frontal Gyrus	Right	38	46	28	4.15	146
LECN	**Parietal lobe**						
	Inferior Parietal Lobule	Left	-54	-58	44	6.28	3110
	Cerebellum Posterior Lobe	Right	40	-72	-34	5.67	647
	Frontal lobe						
	Middle Frontal Gyrus	Left	-44	18	40	5.51	889
	Middle Frontal Gyrus	Left	-42	50	-2	5.26	549
	Frontal lobe						
	Superior Frontal Gyrus	Left	-14	66	24	4.93	169
	Parietal lobe						
	Inferior parietal lobule	Right	42	-66	48	4.65	137
	Temporal lobe						
	Middle Temporal Gyrus	Left	-60	-40	-6	4.5	539
	Frontal lobe						
	Inferior Frontal Cyrus	Left	-54	24	-2	4.48	189
	Cerebellum Anterior Lobe	Left	0	-44	-16	4.92	191
RECN	**Parietal lobe**						
	Inferior Parietal Lobule	Right	52	-50	42	5.83	2966
	Parietal lobe						
	Middle Frontal Gyrus	Right	54	16	36	5.68	4693
	Parietal lobe						
	Inferior Parietal Lobule	Left	-48	-52	44	4.8	253
	Temporal lobe						
	Middle Temporal Gyrus	Right	64	-32	-10	4.78	486
	Cerebellum Posterior Lobe	Left	-36	-66	-42	4.77	241
Sensorimotor	**Parietal lobe**						
	Postcentral Gyrus	Left	-52	-20	54	5.99	3535
	Frontal lobe						
	Precentral Gyrus	Right	44	-6	60	5.14	2207
Primary Visual	**Occipital Lobe**						
	Lingual	Right	18	-70	-12	5.28	4673
	Parietal lobe						
	Postcentral Gyrus	Left	-46	-30	40	5.99	3230
	Frontal lobe						
	Sub-Gyral	Right	26	0	52	5.24	375
	Middle Frontal Gyrus	Left	-28	4	48	5.0	410
	Parietal lobe						
	Precuneus	Right	26	-66	8	4.4	1359
	Frontal lobe						
	Inferior Frontal Gyrus	Left	-46	2	32	4.16	124
Precuneus	**Parietal lobe**						
	Precuneus	Right	14	-68	36	6.19	4624
	Inferior Parietal Lobule	Left	-34	-58	38	4.76	329

[a]Montreal Neurologic Institute coordinates in the local point maximal activation included in the cluster; [b]Activation differences were considered significant at height threshold ($p < 0.001$) and extent threshold of a minimum cluster size. DMN = Default Mode Network; LECN = Left Executive Control Network; RECN = Right Executive Control Network.

DISCUSSION AND CONCLUSIONS

5.1. Hemodynamic responses towards IAPS and IRI

Deficiency in the expression of emotions is one of the features that most impairs the socialization of patients with schizophrenia and constitutes a major challenge for the treatment of this psychiatric disorder. In our study, we sought to identify the functional MRI correlates associated with empathy impairments in patients with the disease. We used task-based fMRI with the IAPS stimulus, an instrument widely applied in affective disorders to study activations during images with positive, negative, and neutral valence. Furthermore, we also aimed to correlate such activations with psychometric scores measured using IRI and PANSS scales.

5.1.1. Overall findings

In this study, we found that, when comparing the positive and the neutral images, patients presented greater activations in the temporal lobe – Superior (TLS), Temporal Gyrus Left (TGL), temporal lobe - Middle Temporal Gyrus Right (MTRG). These results are in line with other studies with larger samples sizes, where authors showed greater activation of brain areas (prefrontal cortical and medial temporal lobe) for positive and neutral images in relation to negative in these patients [124, 125]. Indeed, the scientific literature showed that the ability to express emotions and consequently social integration is closely related to the function of the limbic circuit, which is deficient in SZP [126]. Although there are other studies that have confirmed the existence of greater activation when viewing neutral images in the left medial temporal cortex in SZP [127], our results were not statistically significant in this region.

We expected to see some activation of the amygdala, which is the main region responsible for negative emotions such as fear, anger, or sadness, frequent symptoms during a crisis [123, 128]. Previous studies showed a greater activation in the right amygdala during the visualization of negative pictures [129]. However, we did not observe any statistically significant activation in the amygdala in our population. The explanation for this observation could be the clinical stability of the patient in our population at the time of the task. In addition, one limitation of this study is the lack of a control group to compare activation in the IAPS task. However, such limitation will be eliminated in the future.

We decided to go further in our research by correlating the dimensions of the IAPS paradigm with the psychological and clinical variables.

5.2. Empathic measure: IRI

To study cognitive empathy in SZP, we used the IRI scale, which has two components: regulate the emotional response of another person at the same time that evaluate the affective cognition of the patient, since it includes the understanding of the emotional perspective of a person, through the feelings experienced by others.

5.2.1. IAPS and total IRI

When we correlated the brain activation using the negative pictures during the IAPS paradigm with the total IRI dimension, a positive correlation was observed between negative compared to neutral contrast pictures of the IAPS paradigm with the total IRI dimension. This result is in line with the literature[130, 131] showing that a higher level of empathy was positively correlated with activity in the areas of the post central left (PCL), Occipital Lobe - Lingual Right – cuneus, frontal lobe- precentral gyrus left (FL-LPCG) precentral gyrus right (FL-RPCG), parietal lobe-left inferior parietal (PL-LIP), temporal lobe-temporal superior gyrus left (TL-LSTG), and parietal lobe (PL)- Precuneus Left during the visualization of negative images. This suggests a considerably higher susceptibility in the emotional field in SZP when they are in negative situations such as fear, anger, or sadness. These brain areas correlated with negative stimulus are involved in limbic circuitry.

IRI scales also correlated positively with activation during the positive images (when compared to the negative ones) in the region of the right MPFC. It was already shown that the frontal cortex is related to emotional processes and that most patients with schizophrenia present alterations in neural circuits at this level [23, 106]. Our findings may represent some evidence of abnormal functioning in cortical-basal circuits such as basal ganglia–thalamostriatal projections and thalamic–cortical–striatal functional loop [132], involved in dopaminergic pathways [81]. However, further studies will be necessary to a better understanding of this phenomenon. Interestingly, empathy correlated positively with working memory. This result reinforces the importance of dopamine in the control of emotions, cognition, and memory [61], emphasizing the dopaminergic theory once again.

5.2.2. Personal discomfort dimension

While using the IRI subscales in the multiple regression analysis, we found a positive correlation between negative pictures (when compared to the neutral ones) with the "personal discomfort" dimension of the IRI scale. This correlation was associated with activations in the middle frontal cortex. Personal discomfort dimension measures the anxiety and discomfort that patients feel when other people are suffering. This aspect might explain why SZP have more difficulties to express compassion in relation to the distressing situations of others. This correlation was associated with the activation of the middle frontal cortex, a region that is related to emotion regulation in SZP [23].

5.2.3. Perspective take dimension

We also found a negative correlation between the activation during positive pictures (when compared to the negative ones) in the limbic and temporal lobes with the "perspective taken" dimension of the IRI scale. These regions were shown to be related to emotional regulation and integration of information in SNC [124]. When we analyzed the opposite contrast, negative > positive in correlation with the same dimension, the correlation was positive, confirming the result above and providing further support for the emphatic impairments in SZP [133, 134].

The results above support the study of Philips et al. [135] where they demonstrated that negative emotions can provoke significant alterations on limbic, Para hippocampal, temporal, and occipital lobes and that these regions are involved in emotional regulation. The same regions were significantly activated for correlations between negatives images and perspective take.

5.3. Psychopathological parameters: PANNS

We used a multiple regression test to determine if the SZP score on the clinical scales was correlated with the different dimensions of the IAPS paradigm.

5.3.1. Positive subscale of PANSS

We observed that there was a positive correlation between the negative > positive contrast with the PANSS positive subscale. Using the general score of the test, we found that higher PANSS-positive scores are associated with greater activation at the left frontal lobe –precentral Gyrus when patients visualize negative images. These results show a

congruence with the findings obtained when analyzing the IAPS and IRI with the same contrast in the same regions. These findings further confirm the involvement of the frontal cortex in disorders related to the emotion [133, 136].

We expected to obtain a positive correlation between the negative subscale of the PANSS and the negative compared to positive/neutral contrast, but this was not observed. There was a negative correlation associated with activation in the regions Cerebellum Anterior Lobe bilaterally, parietal lobe- postcentral gyrus right, Sub lobar - Insula right, Right cerebellum posterior lobe. This finding may be related to the fact that the patients were at a more stabilized stage. Thus, this study should be replicated in naïve patients.

5.4. Functional connectivity using rs-fMRI

In our study, patients also underwent a resting-state fMRI acquisition. Using this data, we could measure functional connectivity in SZP at rest. Using MELODIC, we found some resting-state networks (Figure 6). However, when we compared connectivity in these RSNs with healthy controls, no significant differences were observed. This inconsistency may be mainly attributed to the short period of resting data collection, the reduced sample size, and the fact that the control group (n = 6) was not well paired with the patients' group (n =12).

Previous works reported changes in brain connectivity in the different networks in these patients, namely reduced connectivity of the middle prefrontal cortex and alteration of the cortical-subcortical networks, including thalamocortical, frontal-limbic, and cortical-cerebellar networks [137]. Furthermore, previous authors demonstrated dysconnectivity [100] between the HC-DLPFC during the realization of cognitive tasks (working memory and n-back tasks) in SZP.

During rs-fMRI, several patterns of activated networks can be observed: DMN, central executive network, and salience network (SN) [111, 112]. The literature reports a reduction in FNC, DMN, and SN networks in patients with schizophrenia [111, 115]. According to Orliac et al. [115], this reduction is localized in the right anterior paracingulate cortex. Regarding SN, the reduction of connectivity is located in the striatum [112, 116]. Other studies also reported changes in functional brain activity in the lateral and medial frontal cortex, thalamus, and hippocampal gyrus [138, 139].

5.5. Limitations

The first limitation of this study is the sample size. However, we must take into consideration the timeframe proposed for the implementation of this study. This study will be continued and more subjects will be recruited to increase the sample size.

For this work, only male patients were included to build a more homogeneous sample and have more cohesive results.

All patients were taking antipsychotic medications at the time of the study. This could have affected our results. Drug naïve patients with the first episode would be an interesting population to target. However, it would slow down the recruitment process. In fact, little is known about the effect of specific antipsychotics on the central nervous system.

5.6. Conclusion

In summary, our results suggest that patients with schizophrenia may have significant difficulties to correctly understand and to deal with the emotions and suffering of other people. Importantly, we could determine that these impairments are related with specific functional brain correlates. The main conclusions from the experimental work developed are:

(1) The ability to express empathy in SZP when they are exposed to positive stimuli is associated with the activation on the temporal-superior lobe;

(2) Higher levels of empathy are associated with greater activation in occipital lobe-pre and post central gyrus, parietal lobe, and temporal lobe. This result may help to understand the emotional regulation process in schizophrenia since these regions are part of the limbic system;

(3) The difficulties to express compassion can be related to the activation of the medial prefrontal cortex, a region that is involved in emotional regulation;

(4) SZP displayed difficulties to control negative emotions, which might impair social integration. However, future research employing multiple methods can help clarifying the empathic and emotional disturbances in schizophrenia, and the psychological and neural mechanisms through which these difficulties ultimately influence psychosocial recovery;

(5) No significant differences in functional connectivity in RSNs were found between the control group and SZP, which may be related to the limited sample size.

REFERENCES

1. Jablensky, A., *The diagnostic concept of schizophrenia: its history, evolution, and future prospects.* Dialogues Clin Neurosci, 2010. **12**(3): p. 271-87.
2. Figueira, M.L., D. Sampaio, and P. Afonso, *Manual de Psiquiatria Clínica*. 2014, Lidel. Lisboa.[aguarda publicação].
3. Blom, J.D. and H.M. van Praag, *Schizophrenia: it's broken and it can't be fixed. A conceptual analysis at the centenary of Bleuler's Dementia praecox oder Gruppe der Schizophrenien.* Isr J Psychiatry Relat Sci, 2011. **48**(4): p. 240-8.
4. Kahlbaum, K.L., *Die Gruppierung der psychischen Krankheiten und die Eintheilung der Seelenstörungen: Entwurf einer historisch-kritischen Darstellung der bisherigen Eintheilungen und Versuch zur Anbahnung einer empirisch-wissenschaftlichen Grundlage der Psychiatrie als klinischer Disciplin*. 1863: Kafemann.
5. Neumärker, K.-J. and A.J. Bartsch, *Karl Kleist (1879–1960)–a pioneer of neuropsychiatry.* History of Psychiatry, 2003. **14**(4): p. 411-458.
6. Kendler, K.S., *An historical framework for psychiatric nosology.* Psychological medicine, 2009. **39**(12): p. 1935-1941.
7. Maatz, A. and P. Hoff, *The birth of schizophrenia or a very modern Bleuler: a close reading of Eugen Bleuler's 'Die Prognose der Dementia praecox' and a re-consideration of his contribution to psychiatry.* History of Psychiatry, 2014. **25**(4): p. 431-440.
8. Almeida, J., et al., *Estudo Epidemiológico Nacional de Saúde Mental. 1. º Relatório.* Lisboa. Faculdade de Ciências Médicas, Universidade Nova de Lisboa. Disponível em: http://www. fcm. unl. pt/main/alldoc/galeria_imagens/Relatorio_Estudo_Saude-Mental_2. pdf, 2013.
9. Mitchell, R.L.C. and S.L. Rossell, *Perception of emotion-related conflict in human communications: What are the effects of schizophrenia?* Psychiatry Research, 2014. **220**(1–2): p. 135-144.
10. Foussias, G. and G. Remington, *Negative Symptoms in Schizophrenia: Avolition and Occam's Razor.* Schizophrenia Bulletin, 2010. **36**(2): p. 359-369.
11. Sadock, B.J., V.A. Sadock, and P. Ruiz, *Compêndio de Psiquiatria-: Ciência do Comportamento e Psiquiatria Clínica*. 2016: Artmed Editora.
12. Association, A.P., *Diagnostic and statistical manual of mental disorders (DSM-5®)*. 2013: American Psychiatric Pub.
13. MacDonald, A.W. and S.C. Schulz, *What We Know: Findings That Every Theory of Schizophrenia Should Explain.* Schizophrenia Bulletin, 2009. **35**(3): p. 493-508.
14. Vied, C., et al., *Transcriptomic analysis of the hippocampus from six inbred strains of mice suggests a basis for sex-specific susceptibility and severity of neurological disorders.* Journal of Comparative Neurology, 2016. **524**(13): p. 2696-2710.
15. Rodríguez-Testal, J.F., S.-C. Cristina, and S. Perona-Garcelán, *From DSM-IV-TR to DSM-5: Analysis of some changes.* International Journal of Clinical and Health Psychology, 2014. **14**(3): p. 221-231.
16. Lawrie, S.M., et al., *Improving classification of psychoses.* The Lancet Psychiatry, 2016. **3**(4): p. 367-374.
17. Frith, C.D., *The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action.* Psychological Medicine, 1987. **17**(3): p. 631-648.
18. Peralta, V. and M.J. Cuesta, *Psychometric properties of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia.* Psychiatry Research. **53**(1): p. 31-40.

19. Emma E.M. Knowles, Anthony S. David, and Abraham Reichenberg, *Processing Speed Deficits in Schizophrenia: Reexamining the Evidence.* American Journal of Psychiatry, 2010. **167**(7): p. 828-835.
20. Keefe, R.E., et al., *Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the catie trial.* Archives of General Psychiatry, 2007. **64**(6): p. 633-647.
21. Roth, R.M., et al., *Apathy in schizophrenia: reduced frontal lobe volume and neuropsychological deficits.* Am J Psychiatry, 2004. **161**(1): p. 157-9.
22. Landin-Romero, R., *Structural and functional brain imaging correlates of first-degree healthy relatives of patients with schizophrenia.*
23. Fahim, C., et al., *Brain activity during emotionally negative pictures in schizophrenia with and without flat affect: An fMRI study.* Psychiatry Research: Neuroimaging, 2005. **140**(1): p. 1-15.
24. Limpo, T., R.A. Alves, and S.L. Castro, *Medir a empatia: Adaptação portuguesa do Índice de Reactividade Interpessoal.* Laboratório de Psicologia, 2010. **8**: p. 171-184.
25. Lehmann, A., et al., *Subjective experience of emotions and emotional empathy in paranoid schizophrenia.* Psychiatry Res, 2014. **220**(3): p. 825-33.
26. Raffard, S., et al., *Impaired ability to imagine future pleasant events is associated with apathy in schizophrenia.* Psychiatry Research, 2013. **209**(3): p. 393-400.
27. Choi, D., et al., *Effect of empathy trait on attention to various facial expressions: evidence from N170 and late positive potential (LPP).* J Physiol Anthropol, 2014. **33**: p. 18.
28. Hooker, C.I., et al., *Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia.* Biological psychiatry, 2011. **70**(12): p. 1169-1178.
29. Davis, M.H., *Measuring individual differences in empathy: Evidence for a multidimensional approach.* Journal of personality and social psychology, 1983. **44**(1): p. 113-126.
30. Quince, T., et al., *Undergraduate medical students' empathy: current perspectives.* Advances in Medical Education and Practice, 2016. **7**: p. 443.
31. GOLDBERG, E.M. and S.L. MORRISON, *Schizophrenia and Social Class.* The British Journal of Psychiatry, 1963. **109**(463): p. 785-802.
32. Vallejo-Nágera, J., *Introducción a la psicopatología y psiquiatría.* Madrid. Ed. Salvat, 1997.
33. Caldas de Almeida, J. and M. Xavier, *Estudo epidemiológico nacional de saúde mental (vol. 1).* Lisboa. Faculdade de Ciências Médicas, da Universidade Nova de Lisboa, 2013.
34. Andlin-Sobocki, P. and W. Rossler, *Cost of psychotic disorders in Europe.* Eur J Neurol, 2005. **12 Suppl 1**: p. 74-7.
35. Gogos, A., et al., *A role for estrogen in schizophrenia: clinical and preclinical findings.* International journal of endocrinology, 2015. **2015**.
36. Leng, C.H., et al., *Estimation of life expectancy, loss-of-life expectancy, and lifetime healthcare expenditures for schizophrenia in Taiwan.* Schizophr Res, 2016. **171**(1-3): p. 97-102.
37. Kim, W., et al., *Mortality in Schizophrenia and Other Psychoses: Data from the South Korea National Health Insurance Cohort, 2002–2013.* Journal of Korean Medical Science, 2017. **32**(5): p. 835-842.

38. del Paciente, S.F., *Consenso sobre la salud física del paciente con esquizofrenia de las Sociedades Españolas de Psiquiatría y de Psiquiatría Biológica.* Actas Esp Psiquiatr, 2008. **36**(5): p. 251-264.
39. Hennekens, C.H., et al., *Schizophrenia and increased risks of cardiovascular disease.* Am Heart J, 2005. **150**(6): p. 1115-21.
40. Olfson, M., et al., *Premature mortality among adults with schizophrenia in the united states.* JAMA Psychiatry, 2015. **72**(12): p. 1172-1181.
41. Brown, S., *Excess mortality of schizophrenia. A meta-analysis.* The British Journal of Psychiatry, 1997. **171**(6): p. 502-508.
42. Hoff, A.L., et al., *Association of estrogen levels with neuropsychological performance in women with schizophrenia.* American Journal of Psychiatry, 2001. **158**(7): p. 1134-1139.
43. Loranger, A.W., *Sex difference in age at onset of schizophrenia.* Archives of general psychiatry, 1984. **41**(2): p. 157-161.
44. Shtasel, D.L., et al., *Gender differences in the clinical expression of schizophrenia.* Schizophrenia research, 1992. **7**(3): p. 225-231.
45. Da Silva, T.L. and A.V. Ravindran, *Contribution of sex hormones to gender differences in schizophrenia: a review.* Asian journal of psychiatry, 2015. **18**: p. 2-14.
46. Seeman, M.V. and M. Lang, *The role of estrogens in schizophrenia gender differences.* Schizophrenia Bulletin, 1990. **16**(2): p. 185.
47. Nancy L. Bryant, et al., *Gender Differences in Temporal Lobe Structures of Patients With Schizophrenia: A Volumetric MRI Study.* American Journal of Psychiatry, 1999. **156**(4): p. 603-609.
48. Kulkarni, J., et al., *Estrogens and men with schizophrenia: Is there a case for adjunctive therapy?* Schizophrenia Research, 2011. **125**(2–3): p. 278-283.
49. Kulkarni, J., et al., *Estradiol for treatment-resistant schizophrenia: a large-scale randomized-controlled trial in women of child-bearing age.* Mol Psychiatry, 2015. **20**(6): p. 695-702.
50. Kulkarni, J., et al., *Estrogen — a potential treatment for schizophrenia.* Schizophrenia Research, 2001. **48**(1): p. 137-144.
51. Goldstein, J.M., *Gender differences in the course of schizophrenia.* Am J Psychiatry, 1988. **145**(6): p. 684-689.
52. Machado Dias, Á., L. Rodrigues, and E. Avelino, *Schizophrenia, genetics, epigenesis, environment: a systematic review of unified etiological hypotheses and genetic profile; and a new algorithm to cope with the main findings.* Avances en Psicología Latinoamericana, 2010. **28**(1): p. 29-41.
53. Merelo, V., et al., *Associating schizophrenia, long non-coding RNAs and neurostructural dynamics.* Frontiers in molecular neuroscience, 2015. **8**: p. 57.
54. Howes, O.D., et al., *The role of genes, stress, and dopamine in the development of schizophrenia.* Biological Psychiatry, 2017. **81**(1): p. 9-20.
55. Lakhan, S.E. and K.F. Vieira, *Schizophrenia pathophysiology: are we any closer to a complete model?* Annals of General Psychiatry, 2009. **8**(1): p. 12.
56. Martin, A., et al., *Copy number deletion burden is associated with cognitive, structural, and resting-state network differences in patients with schizophrenia.* Behavioural brain research, 2014. **272**: p. 324-334.
57. McNeil, T.F., E. Cantor-Graae, and B. Ismail, *Obstetric complications and congenital malformation in schizophrenia.* Brain Res Brain Res Rev, 2000. **31**(2-3): p. 166-78.

58. Fendt, M., et al., *Behavioural alterations in rats following neonatal hypoxia and effects of clozapine: implications for schizophrenia.* Pharmacopsychiatry, 2008. **41**(4): p. 138-45.
59. Brisch, R., et al., *The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue.* Frontiers in psychiatry, 2014. **5**: p. 47.
60. Blum, K., et al., *Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): a commentary.* Theoretical Biology and Medical Modelling, 2008. **5**(1): p. 24.
61. Goldman-Rakic, P.S., E.C. Muly Iii, and G.V. Williams, *D_1 receptors in prefrontal cells and circuits.* Brain Research Reviews, 2000. **31**(2-3): p. 295-301.
62. Frank, M.J. and R.C. O'reilly, *A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol.* Behavioral neuroscience, 2006. **120**(3): p. 497.
63. Welberg, L., *Neuroanatomy: A split (mid) brain for dopamine.* Nature Reviews Neuroscience, 2008. **9**(5): p. 326-326.
64. Bressan, R.A. and L.S. Pilowsky, *Hipotese glutamatergica da esquizofrenia.* Revista Brasileira de Psiquiatria, 2003. **25**(3): p. 177-183.
65. Abi-Dargham, A., et al., *Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort.* American Journal of Psychiatry, 1998. **155**(6): p. 761-767.
66. Laruelle, M., et al., *Increased dopamine transmission in schizophrenia: relationship to illness phases.* Biological psychiatry, 1999. **46**(1): p. 56-72.
67. Howes, O.D. and S. Kapur, *The Dopamine Hypothesis of Schizophrenia: Version III—The Final Common Pathway.* Schizophrenia Bulletin, 2009. **35**(3): p. 549-562.
68. Meltzer, H.Y. and S.R. McGurk, *The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia.* Schizophrenia bulletin, 1999. **25**(2): p. 233-256.
69. Dao-Castellana, M.-H., et al., *Presynaptic dopaminergic function in the striatum of schizophrenic patients.* Schizophrenia research, 1997. **23**(2): p. 167-174.
70. Friston, K.J., *The disconnection hypothesis.* Schizophrenia Research, 1998. **30**(2): p. 115-125.
71. Neto, A., et al., *Physiopathology of schizophrenia: current aspects.* Archives of Clinical Psychiatry (São Paulo), 2007. **34**: p. 198-203.
72. Shireen, E., *Experimental treatment of antipsychotic-induced movement disorders.* Journal of Experimental Pharmacology, 2016. **8**: p. 1.
73. Nakajima, S., et al., *Neuroimaging findings in treatment-resistant schizophrenia: a systematic review: Lack of neuroimaging correlates of treatment-resistant schizophrenia.* Schizophrenia research, 2015. **164**(0): p. 164-175.
74. Reif, A., et al., *Neural stem cell proliferation is decreased in schizophrenia, but not in depression.* Mol Psychiatry, 2006. **11**(5): p. 514-522.
75. Wakade, C.G., et al., *Atypical neuroleptics stimulate neurogenesis in adult rat brain.* Journal of neuroscience research, 2002. **69**(1): p. 72-79.
76. Lieberman , J.A., et al., *Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia.* New England Journal of Medicine, 2005. **353**(12): p. 1209-1223.
77. Caligiuri, M.P., D.V. Jeste, and J.P. Lacro, *Antipsychotic-Induced Movement Disorders in the Elderly.* Drugs & Aging, 2000. **17**(5): p. 363-384.

78. Gallhofer, B., et al., *Cognitive dysfunction in schizophrenia: comparison of treatment with atypical antipsychotic agents and conventional neuroleptic drugs.* European Neuropsychopharmacology, 1996. **6**: p. 13-20.
79. Leucht, S., et al., *Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis.* The Lancet. **373**(9657): p. 31-41.
80. Correll, C.U., et al., *Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials.* Schizophrenia Bulletin, 2009. **35**(2): p. 443-457.
81. Weickert, T.W., K.M. Allen, and C.S. Weickert, *Potential Role of Oestrogen Modulation in the Treatment of Neurocognitive Deficits in Schizophrenia.* CNS drugs, 2016. **30**(2): p. 125-133.
82. Fervaha, G., et al., *Lack of association between dopaminergic antagonism and negative symptoms in schizophrenia: a positron emission tomography dopamine D2/3 receptor occupancy study.* Psychopharmacology, 2016. **233**(21-22): p. 3803-3813.
83. Williamson, P.C. and J.M. Allman, *A framework for interpreting functional networks in schizophrenia.* Frontiers in Human Neuroscience, 2012. **6**: p. 184.
84. Gore, J.C., *Principles and practice of functional MRI of the human brain.* Journal of Clinical Investigation, 2003. **112**(1): p. 4-9.
85. Glover, G.H., *Overview of Functional Magnetic Resonance Imaging.* Neurosurgery clinics of North America, 2011. **22**(2): p. 133-139.
86. Honey, G.D., et al., *Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia.* Proceedings of the National Academy of Sciences, 1999. **96**(23): p. 13432-13437.
87. Yan, S., et al., *An Approximation Approach to Measurement Design in the Reconstruction of Functional MRI Sequences*, in *Brain and Health Informatics: International Conference, BHI 2013, Maebashi, Japan, October 29-31, 2013. Proceedings*, K. Imamura, et al., Editors. 2013, Springer International Publishing: Cham. p. 115-125.
88. Soares, J.M., et al., *A Hitchhiker's Guide to Functional Magnetic Resonance Imaging.* Frontiers in Neuroscience, 2016. **10**.
89. Gil, V. and C. Geraldes, *Ressonância Magnética Nuclear: Fundamentos, Métodos e Aplicações. 1987.* Lisboa: Fundação Calouste Gulbenkian. **1012**.
90. Cariaga-Martinez, A., J. Saiz-Ruiz, and R. Alelú-Paz, *From Linkage Studies to Epigenetics: What We Know and What We Need to Know in the Neurobiology of Schizophrenia.* Front Neurosci, 2016. **10**.
91. Palha, J.A., et al., *Do genes and environment meet to regulate cerebrospinal fluid dynamics? Relevance for schizophrenia.* Frontiers in cellular neuroscience, 2012. **6**: p. 31.
92. Vita, A., L. De Peri, and E. Sacchetti, *Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies.* Bipolar disorders, 2009. **11**(8): p. 807-814.
93. Okada, N., et al., *Abnormal asymmetries in subcortical brain volume in schizophrenia.* Mol Psychiatry, 2016. **21**(10): p. 1460-1466.
94. Bähner, F. and A. Meyer-Lindenberg, *Hippocampal–prefrontal connectivity as a translational phenotype for schizophrenia.* European Neuropsychopharmacology, 2017.

95. Knöchel, C., et al., *Multimodal assessments of the hippocampal formation in schizophrenia and bipolar disorder: Evidences from neurobehavioral measures and functional and structural MRI.* NeuroImage : Clinical, 2014. **6**: p. 134-144.
96. van Erp, T.G., et al., *Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium.* Molecular psychiatry, 2016. **21**(4): p. 547-553.
97. Fujiwara, H., W. Yassin, and T. Murai, *Neuroimaging studies of social cognition in schizophrenia.* Psychiatry and clinical neurosciences, 2015. **69**(5): p. 259-267.
98. Lindquist, M.A., *The statistical analysis of fMRI data.* Statistical Science, 2008: p. 439-464.
99. Skudlarski, P., et al., *Brain Connectivity Is Not Only Lower but Different in Schizophrenia: A Combined Anatomical and Functional Approach.* Biological Psychiatry, 2010. **68**(1): p. 61-69.
100. Pettersson-Yeo, W., et al., *Dysconnectivity in schizophrenia: Where are we now?* Neuroscience & Biobehavioral Reviews, 2011. **35**(5): p. 1110-1124.
101. Liu, B., et al., *The Impact of MIR137 on Dorsolateral Prefrontal–Hippocampal Functional Connectivity in Healthy Subjects.* Neuropsychopharmacology, 2014. **39**(9): p. 2153-2160.
102. Rasetti, R., et al., *Altered cortical network dynamics: A potential intermediate phenotype for schizophrenia and association with znf804a.* Archives of General Psychiatry, 2011. **68**(12): p. 1207-1217.
103. Lynall, M.-E., et al., *Functional Connectivity and Brain Networks in Schizophrenia.* The Journal of Neuroscience, 2010. **30**(28): p. 9477-9487.
104. Horan, W.P., et al., *Impaired Emotion Regulation in Schizophrenia: Evidence From Event-Related Potentials.* Psychological medicine, 2013. **43**(11): p. 2377-2391.
105. Lang, P.J., M.M. Bradley, and B.N. Cuthbert, *International affective picture system (IAPS): Technical manual and affective ratings.* NIMH Center for the Study of Emotion and Attention, 1997: p. 39-58.
106. Takahashi, H., et al., *An fMRI study of differential neural response to affective pictures in schizophrenia.* NeuroImage, 2004. **22**(3): p. 1247-1254.
107. Schneider, F., et al., *Differential amygdala activation in schizophrenia during sadness.* Schizophrenia research, 1998. **34**(3): p. 133-142.
108. Gur, R.E., et al., *An fMRI study of facial emotion processing in patients with schizophrenia.* American Journal of Psychiatry, 2002. **159**(12): p. 1992-1999.
109. Mwansisya, T.E., et al., *Task and resting-state fMRI studies in first-episode schizophrenia: A systematic review.* Schizophr Res, 2017.
110. Kraguljac, N.V., A. Srivastava, and A.C. Lahti, *Memory Deficits in Schizophrenia: A Selective Review of Functional Magnetic Resonance Imaging (fMRI) Studies.* Behavioral Sciences, 2013. **3**(3): p. 330-347.
111. Palaniyappan, L., et al., *Regional contraction of brain surface area involves three large-scale networks in schizophrenia.* Schizophrenia research, 2011. **129**(2): p. 163-168.
112. White, T.P., et al., *Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia.* Schizophrenia Research, 2010. **123**(2–3): p. 105-115.
113. Palaniyappan, L. and P.F. Liddle, *Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction.* Journal of Psychiatry & Neuroscience : JPN, 2012. **37**(1): p. 17-27.

114. Zhou, Y., et al., *Functional disintegration in paranoid schizophrenia using resting-state fMRI.* Schizophrenia research, 2007. **97**(1): p. 194-205.
115. Orliac, F., et al., *Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia.* Schizophrenia research, 2013. **148**(1): p. 74-80.
116. Tu, P.-C., et al., *Cortico-striatal disconnection within the cingulo-opercular network in schizophrenia revealed by intrinsic functional connectivity analysis: A resting fMRI study.* NeuroImage, 2012. **59**(1): p. 238-247.
117. Garcia, I.Q., et al., *Propriedades psicométricas da versão Torga do Teste Stroop.* 2016.
118. *Selective Reminding and Free and Cued Selective Reminding in Mild Cognitive Impairment and Alzheimer Disease.* Applied Neuropsychology: Adult, 2016. **23**(2): p. 85-93.
119. Kay, S.R., A. Flszbein, and L.A. Opfer, *The positive and negative syndrome scale (PANSS) for schizophrenia.* Schizophrenia bulletin, 1987. **13**(2): p. 261.
120. Buschke, H., *Selective reminding for analysis of memory and learning.* Journal of Verbal Learning and Verbal Behavior, 1973. **12**(5): p. 543-550.
121. Beatty, W.W., et al., *Further validation of constructs from the selective reminding test.* J Clin Exp Neuropsychol, 1996. **18**(1): p. 52-5.
122. Lang, P., M. Bradley, and B. Cuthbert, *Technical Report A-6, International Affective Picture System (IAPS): Digitized Photographs, Instruction Manual and Affective Ratings*. 2005, Gainesville, FL.: University of Florida.
123. Rosenblau, G., et al., *Functional neuroanatomy of emotion processing in major depressive disorder is altered after successful antidepressant therapy.* Journal of psychopharmacology, 2012: p. 0269881112450779.
124. Eack, S.M., et al., *Fronto-Limbic Brain Dysfunction during the Regulation of Emotion in Schizophrenia.* PLoS ONE, 2016. **11**(3): p. e0149297.
125. Holt, D.J., et al., *Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia.* Schizophrenia Research, 2006. **82**(2): p. 153-162.
126. Zald, D.H., *The human amygdala and the emotional evaluation of sensory stimuli.* Brain Res Brain Res Rev, 2003. **41**(1): p. 88-123.
127. Holt, D.J., et al., *Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia.* Schizophr Res, 2006. **82**(2-3): p. 153-62.
128. Bruneau, E.G., N. Jacoby, and R. Saxe, *Empathic control through coordinated interaction of amygdala, theory of mind and extended pain matrix brain regions.* NeuroImage, 2015. **114**: p. 105-119.
129. Pankow, A., et al., *Altered amygdala activation in schizophrenia patients during emotion processing.* Schizophr Res, 2013. **150**(1): p. 101-6.
130. Henson, R., *What can functional neuroimaging tell the experimental psychologist?* Q J Exp Psychol A, 2005. **58**(2): p. 193-233.
131. Eklund, A., et al., *Does parametric fMRI analysis with SPM yield valid results? An empirical study of 1484 rest datasets.* Neuroimage, 2012. **61**(3): p. 565-78.
132. Cavallaro, R., et al., *Basal-corticofrontal circuits in schizophrenia and obsessive-compulsive disorder.* Biological Psychiatry, 2003. **54**(4): p. 437-443.
133. Sparks, A., et al., *Social cognition, empathy and functional outcome in schizophrenia.* Schizophr Res, 2010. **122**(1-3): p. 172-8.
134. Corbera, S., et al., *Physiological evidence of a deficit to enhance the empathic response in schizophrenia.* Eur Psychiatry, 2014. **29**(8): p. 463-72.

135. Phillips, M.L., C.D. Ladouceur, and W.C. Drevets, *A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder.* Molecular psychiatry, 2008. **13**(9): p. 829-857.
136. Vaina, L.M., et al., *When does subliminal affective image priming influence the ability of schizophrenic patients to perceive face emotions?* Med Sci Monit, 2014. **20**: p. 2788-98.
137. Woodward, N.D., H. Karbasforoushan, and S. Heckers, *Thalamocortical dysconnectivity in schizophrenia.* Am J Psychiatry, 2012. **169**(10): p. 1092-9.
138. Minzenberg, M.J., et al., *Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia.* Archives of general psychiatry, 2009. **66**(8): p. 811-822.
139. Ragland, J.D., et al., *Prefrontal activation deficits during episodic memory in schizophrenia.* American Journal of Psychiatry, 2009. **166**(8): p. 863-874.

ANNEXES

Functional brain correlates of cognitive and affective impairments in male patients with Schizophrenia

Coordenador do projecto: Prof. Doutor João Bessa

Escola de Ciências da Saúde

Instituto de Investigação em Ciências da Vida e da Saúde

Universidade do Minho

ADMINISTRAÇÃO DAS PROVAS

1º Consentimento informado

2º Caracterização sociodemográfica

3º Caracterização Clínica

4º PANSS- Positive and negative Syndrome Scale

5º Índice de Reatividade Interpessoal (Avaliação da Afetividade)

6º Stroop test (Avaliação da função executiva)

7º WAIS- III - Digit simbol (Avaliação da Cognição)

8º WAIS-III- Digit Span (Avaliação da Cognição)

9º SRT (Avaliação da retenção da memória)

DECLARAÇÃO DE CONSENTIMENTO INFORMADO

Considerando a "Declaração de Helsínquia" da Associação Médica Mundial

(Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996 e Edimburgo 2000)

Nome do Estudo: Sono, Stress e Cognição nas Doenças Psiquiátricas

O meu nome é João Bessa e sou Médico Especialista do Serviço de Psiquiatria do Hospital de Braga e Professor e Investigar no Escola de Ciências da Saúde da Universidade do Minho, encontrando-me a desenvolver a investigação na área das Neurociências Clínicas. Gostaria de o(a) o convidar a participar num projeto de investigação no âmbito do Centro Clínico Académico que se intitula Sono, Stress e Cognição nas Doenças Psiquiátricas.

1 – Introdução

A tomada de decisão é o processo universal que permite aos animais escolherem entre diferentes alternativas, baseando-se no valor que atribuem a cada uma. As decisões podem ser reguladas através do uso da atenção, linguagem e controle executivo. Esta regulação ocorre, por exemplo, quando tentamos reduzir o nosso apetite por um alimento que nos é apetecível mas que não queremos ingerir.

Os sistemas de regulação do sono e apetite são fundamentais para a manutenção do equilíbrio dos organismos vivos. As observações clínicas e os estudos de investigação têm demonstrado de forma consistente relações entre a alteração desses sistemas e o surgimento e desenvolvimento de várias patologias, nomeadamente as doenças psiquiátricas. De facto, verifica-se que um grande número de patologias psiquiátricas está associado a alterações do sono e do apetite, mas apesar da sua relevância clínica, desconhece-se qual o substrato neurobiológico para estas alterações e está por esclarecer se são a causa ou uma consequência do desenvolvimento dessas doenças psiquiátricas.

O presente estudo tem como objetivo perceber como é que o padrão de sono pode alterar a regulação cognitiva da tomada de decisão e a sua relação com diferentes patologias psiquiátricas. Este pretende ainda caracterizar com maior detalhe o funcionamento de algumas áreas cerebrais durante a realização de uma tarefa específica. Para tal, procederemos à realização de uma Ressonância Magnética associada a uma tarefa de regulação da tomada decisão. Adicionalmente, pretendemos caracterizar os participantes no estudo através da realização de testes neuropsicológicos. A par da informação proveniente destes testes, serão recolhidos dados importantes relativos a demografia e antropometria, bem como a análises laboratoriais.

Nunca em nenhuma fase do estudo serão divulgados dados confidenciais do sujeito. Quando a informação for analisada não será possível saber a identificação dos indivíduos envolvidos no estudo. No entanto, os dados poderão ser observados por um Comité de Revisão Ética e podem ser publicados em jornais científicos ou em outros lugares sem que a sua identidade seja revelada.

Você é livre para optar por participar no estudo. Uma vez integrado no estudo pode também a qualquer momento abandoná-lo, sem qualquer tipo de prejuízo.

2 – Autorização

Eu, abaixo-assinado, (nome completo do participante) _____
_____, compreendi a explicação que me foi fornecida, por escrito e verbalmente, da investigação que se tenciona realizar, para qual é pedida a minha participação. Foi-me dada oportunidade de fazer as perguntas que julguei necessárias, e para todas obtive resposta satisfatória.

Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação que me foi prestada versou os objectivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de decidir livremente aceitar ou recusar a todo o tempo a minha participação no estudo. Sei que se recusar não haverá qualquer prejuízo na assistência que me é prestada.

Foi-me dado todo o tempo de que necessitei para reflectir sobre esta proposta de participação.

Nestas circunstâncias, decido livremente aceitar participar neste projecto de investigação, tal como me foi apresentado pelo investigador(a).

Nome do Participante

_____

Assinatura do Participante

_____

Data

_____

Assinatura do Coordenador do estudo

_____

Data

_____

Assinatura da pessoa que obteve o consentimento

_____

Data

_____

Caracterização Sócio-Demográfica

Identificação / Código: _____ **Data** (DD/MM/AAAA): ____/____/_____

Sexo: _____ **Idade:** _____ **Data de Nascimento** (DD/MM/AAAA):____/____/_____

Descrição da situação escolar:

1. **Escolaridade** (nº de anos) _____

1.1. Qual o nível de escolaridade mais elevado que completou?

- **a)** Ensino Básico - 1º Ciclo (1) ◯
- **b)** Ensino Básico - 2º Ciclo (2) ◯
- **c)** Ensino Básico - 3º Ciclo (3) ◯
- **d)** Ensino Secundário (4) ◯
- **e)** Ensino Pós-Secundário (5) ◯
- **f)** Ensino Superior (6) ◯
- **g)** Ainda não completou nenhum nível de ensino / a estudar (95) ◯
- **h)** Nenhum (96) ◯
- **i)** Outro (inclui diploma obtido no estrangeiro) (97) ◯

1.2. Sabe ler? Sim ◯ Não ◯

1.3. Sabe escrever? Sim ◯ Não ◯

1.4. Observações (p.e: área de formação ou frequenta novas oportunidades): _____

_____

Descrição da área de residência:

2. **Área**

- **a)** Grande cidade (city) (0) ◯
- **b)** Cidade (town) (1) ◯
- **c)** Subúrbios (2) ◯
- **d)** Rural (ex.: aldeia ou vila) (3) ◯
- **e)** Não administrado (4) ◯

2.1. Qual (localidade): _____

Naturalidade:

3. **Local onde nasceu** _____

3.1. Observações: _____

3.2. Local onde nasceu o pai: _____

3.3. Observações: _____

3.4. Local onde nasceu a mãe: _____

3.5. Observações: _____

Descrição da raça e/ou etnia:

1. **Raça/Etnia** _____
2. **Em que país nasceu?** _____
3. **Caso não tenha nascido em Portugal, em que ano veio viver para Portugal**? _____
4. **Observações**_____

_____

Descrição da composição familiar:

1. **Estado Civil**

- **a)** Solteiro (0) ◯
- **b)** Casado (1) ◯
- **c)** Divorciado (2) ◯
- **d)** Viúvo (3) ◯
- **e)** Não administrado (4) ◯

2. **Situação residencial**

- **a)** Sozinho (0) ◯
- **b)** Com companheiro (1) ◯
- **c)** Com familiares (2) ◯
- **d)** Outros (3) ◯
- **e)** Não administrado (4) ◯

2.1. Número de pessoas agregado familiar?____

2.2. Descrição do agregado familiar: _____

_____

_____

2.3. Os seus pais ainda estão vivos atualmente?

Sim (1) ◯; Não (2) ◯; Não se aplica (99) ◯

2.4. Quantos irmãos têm? ____

2.5. Quantos filhos tem? ____

2.6. Quantos netos tem? ____

3. **Observações:** _____

_____

_____

Descrição da ocupação primária ou trabalho:

1. **Ocupação primária**

a) Empregado(a) a tempo inteiro (1) ◯
b) Empregado(a) a tempo parcial (2) ◯
c) Trabalhador por conta própria (3) ◯
d) Desempregado(a) (4) ◯
e) Reformado(a) (5) ◯
f) Doença permanente/Incapacidade (6) ◯
g) Doméstico(a) ou a cuidar da família (7) ◯
h) Outro (8) ◯

2. **Qual a melhor opção que descreve a sua ocupação primária? Se reformado, a ocupação primária que tinha.**

a) Quadro superior da administração pública, dirigente e quadro superior de empresas (1) ◯
b) Profissional liberal (2) ◯
c) Técnico profissional de nível intermédio (3) ◯
d) Pessoal administrativo e similares (4) ◯
e) Pessoal dos serviços e vendedores (5) ◯
f) Trabalhador qualificado da agricultura e pescas (6) ◯
g) Operário, artífice e trabalhador similar (7) ◯
h) Operador de instalações e máquinas, e trabalhador da montagem (8) ◯
i) Trabalhador não qualificado (9) ◯
j) Forças armadas (10) ◯

2.1 Duração de ocupação (anos) _____

2.2 Função desempenhada? _____

3. **Observações:** _____
_____

Lateralidade

a) Direita (0) ◯
b) Esquerda (1) ◯
c) Ambidextro (2) ◯

Outras anotações: _____
_____
_____
_____
_____

Apoio social

1. **Quantas pessoas estão próximas de si o suficiente para que possa contar com elas se algum problema pessoal grave lhe acontecer?**

a) Nenhuma (0) ◯
b) 1 a 2 pessoas (1) ◯
c) 3 a 5 pessoas (2) ◯
d) Mais de 5 pessoas (3) ◯
e) Não aplicável (4) ◯

2. **Qual o interesse e envolvimento dessas pessoas relativamente às suas experiencias do dia a dia?**

a) Nenhum (0) ◯
b) Reduzido (1) ◯
c) Não tenho a certeza (2) ◯
d) Algum (3) ◯
e) Não aplicável (4) ◯

f) Neste momento, qual o seu nível de satisfação com o apoio social em que está sendo dedicado?

a) Nada satisfeito (0) ◯
b) Pouco satisfeito (1) ◯
c) Muito satisfeito (2) ◯
d) Não aplicável (4) ◯

Outras anotações: _____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Avaliação Clínica

Nome:_____ **Código:** _____ **Data de realização:**____/___/___ **Idade:**_____

Hábitos de consumo (Assinalar a opção correcta)						
Tabaco:	Sim:	Não:	Ex:	**Bebidas alcoólicas:**	Sim:	Não:
Quantidade (maços):	**Tempo de fumador** (anos):			**Tipo:**	**Quantidade diária (ml):**	
Observações: _____				Vinho		
				Cerveja		
				Bagaço		
				Bebidas destiladas		
				Outras:		

Terapeutica habitual (assinalar a opção correcta)		
Antipsicóticos	Sim – Qual?	Não
Antidepressivos	Sim– Qual?	Não
Psicofármacos	Sim – Qual?	Não
Depressores do SNC	Sim– Qual?	Não
Anti-hipertensores	Sim– Qual?	Não
Medicação colesterol	Sim– Qual?	Não
Anti-diabéticos orais	Sim– Qual?	Não
Aspirina	Sim– Qual?	Não
Outra (qual?)	Sim– Qual?	Não

Patologias conhecidas (assinalar quais)					
Esquizofrenia	Sim	Não	**Doença cerebrovascular**	Sim	Não
Depressão	Sim	Não	**Insuficiência renal crónica**	Sim	Não
Outras doenças psiquiátricas	Sim	Não	**Cancro**	Sim	Não
Diabetes Mellitus	Sim	Não	**Doenças endócrinas**	Sim	Não
Hipertensão arterial	Sim	Não	**Doença neurológica**	Sim	Não
Doença cardíaca	Sim	Não	**Outra (qual?)**	Sim	Não

Especificar: _____

Revisão de cirurgia e/ou internamentos (assinalar a opção correta)				
Internamento	Últimos 6 meses	6 a 12 meses	12 a 24 meses	Mais de 24 meses
Cirurgia	Últimos 6 meses	6 a 12 meses	12 a 24 meses	Mais de 24 meses

Observações/Motivo (ESPECIFICAR DATA): _____

Evolução da Doença

Com que idade ocorreu o primeiro episódio de esquizofrenia? _____

Aproximadamente quantas crises já sofreu? _____

Na familia existe alguem que sofra da mesma doença? _____

Anotações relevantes

Observações: _____

Positive and Negative Syndrome Scale Schizophrenia - PANSS

Nome:_____ **Código:** _____ **Data de realização:**____/___/___

Subescala positiva	Ausência	Mínimo	Ligeiro	Moderado	Moderadamente grave	Grave	Extremamente grave
P1 – Delírios	1	2	3	4	5	6	7
P2 - Desorganização conceitual	1	2	3	4	5	6	7
P3 - Comportamento alucinatório	1	2	3	4	5	6	7
P4 - Excitação	1	2	3	4	5	6	7
P5 – Grandeza	1	2	3	4	5	6	7
P6 - Desconfiança	1	2	3	4	5	6	7
P7 - Hostilidade	1	2	3	4	5	6	7
TOTAL:							

Subescala negativa	Ausência	Mínimo	Ligeiro	Moderado	Moderadamente grave	Grave	Extremamente grave
N1 - Embotamento afetivo	1	2	3	4	5	6	7
N2 – Isolamento social	1	2	3	4	5	6	7
N3 - Comunicação pobre	1	2	3	4	5	6	7
N4 - Isolamento social passivo/apático	1	2	3	4	5	6	7
N5 - Dificuldade pensamento abstrato	1	2	3	4	5	6	7
N6 - Falta de espontaneidade e fluxo verbal	1	2	3	4	5	6	7
N7 - Pensamento estereotipado	1	2	3	4	5	6	7
TOTAL:							

Subescala geral de psicopatologia	Ausência	Mínimo	Ligeiro	Moderado	Moderadamente grave	Grave	Extremamente grave
G1 - Preocupação somática	1	2	3	4	5	6	7
G2 - Ansiedade	1	2	3	4	5	6	7
G3 – Sentimentos de culpa	1	2	3	4	5	6	7
G4 - Tensão	1	2	3	4	5	6	7
G5 - Maneirismo/postura	1	2	3	4	5	6	7
G6 - Depressão	1	2	3	4	5	6	7
G7 - Retardamento motor	1	2	3	4	5	6	7
G8 - Falta de cooperação	1	2	3	4	5	6	7
G9 - Conteúdo incomum pensamento	1	2	3	4	5	6	7
G10 - Desorientação	1	2	3	4	5	6	7
G11 – Défice atenção	1	2	3	4	5	6	7
G12 – Falta de julgamento e insight	1	2	3	4	5	6	7
G13 - Distúrbio da vontade	1	2	3	4	5	6	7
G14 - Pobre controlo de impulsos	1	2	3	4	5	6	7
G15 - Preocupação	1	2	3	4	5	6	7
G16 - Evitamento social ativo	1	2	3	4	5	6	7
TOTAL:							

Índice de Reactividade Interpessoal

Mark Davis, 1983 (adaptação portuguesa de Teresa Limpo, Rui A. Alves e São Luís Castro, 2010)

Nome:_____ **Código:** _____ **Data de realização:**____/__/__

Legenda. [i] item invertido; [TP] Tomada de Perspectiva; [PE] Preocupação Empática; [DP] Desconforto Pessoal; [F] Fantasia.

COMPORTAMENTO	A	B	C	D	E
01. Tenho muitas vezes sentimentos de ternura e preocupação pelas pessoas menos afortunadas do que eu. [PE]	A	B	C	D	E
02. De vez em quando tenho dificuldade em ver as coisas do ponto de vista dos outros. [TP] [i]	A	B	C	D	E
03. Às vezes, não sinto muita pena quando as outras pessoas estão a ter problemas. [PE] [i]	A	B	C	D	E
04. Facilmente me deixo envolver nos sentimentos das personagens de um romance. [F]	A	B	C	D	E
05. Em situações de emergência, sinto-me desconfortável e apreensivo/apreensiva. [DP]	A	B	C	D	E
06. Habitualmente mantenho a objectividade ao ver um filme ou um teatro e não me deixo envolver por completo. (F) [i]	A	B	C	D	E
07. Quando há desacordo, tento atender a todos os pontos de vista antes de tomar uma decisão. [TP]	A	B	C	D	E
08. Quando vejo que se estão a aproveitar de uma pessoa, sinto vontade de a proteger. [PE]	A	B	C	D	E
09. Por vezes tento compreender melhor os meus amigos imaginando a sua perspectiva de ver as coisas. [TP]	A	B	C	D	E
10. É raro ficar completamente envolvido/envolvida num bom livro ou filme. [F] [i]	A	B	C	D	E
11. Quando vejo alguém ficar ferido, tendo a permanecer calmo/calma. [DP] [i]	A	B	C	D	E
12. As desgraças dos outros não me costumam perturbar muito. [PE] [i]	A	B	C	D	E
13. Depois de ver um filme ou um teatro, sinto-me como se tivesse sido uma das personagens. [F]	A	B	C	D	E
14. Estar numa situação emocional tensa assusta-me. [DP]	A	B	C	D	E
15. Geralmente sou muito eficaz a lidar com emergências. [DP] [i]	A	B	C	D	E
16. Fico muitas vezes emocionado/emocionada com coisas que vejo acontecer. [PE]	A	B	C	D	E
17. Acredito que uma questão tem sempre dois lados e tento olhar para ambos. [TP]	A	B	C	D	E
18. Descrever-me-ia como uma pessoa de coração mole. [PE]	A	B	C	D	E
19. Quando vejo um bom filme, consigo facilmente pôr-me no lugar do protagonista. [F]	A	B	C	D	E
20. Tendo a perder o controlo em situações de emergência. [DP]	A	B	C	D	E
21. Quando estou aborrecido/aborrecida com alguém, geralmente tento pôr-me no seu lugar por um momento. [TP]	A	B	C	D	E
22. Quando estou a ler uma história ou um romance interessante, imagino como me sentiria se aqueles acontecimentos se tivessem passado comigo.[F]	A	B	C	D	E
23. Quando vejo alguém numa emergência a precisar muito de ajuda, fico completamente perdido/perdida. [DP]	A	B	C	D	E
24. Antes de criticar alguém, tento imaginar como me sentiria se estivesse no seu lugar. [TP]	A	B	C	D	E
TOTAL:					

Folha de Registo

Teste Stroop: Palavras

Identificação/Código:_____ Data de avaliação: __/__/__

Instruções: Aqui temos palavras escritas. Queria que me lesse estas palavras em voz alta, o mais depressa que puder. Comece no início da 1ª coluna, quando acabar passe à 2ª, depois à 3ª e finalmente à última. Se se enganar, corrija e continue. Depois de eu dizer "Pode começar", comece. Entendido? Então atenção: Pode começar!

Tempo: Dê o sinal de partida ao mesmo tempo que aciona o cronómetro. O tempo limite é de 45 segundos. Diga: "Pode parar", quando o tempo limite chegar ao fim.

Cotação: Marca-se com um visto ✔ as respostas corretas, com uma cruz ☒ as incorretas e com um **C** as correções espontâneas.

1 verde ___	**26** verde___	**51** verde___	**76** verde___	**101** azul___
2 azul ___	**27** azul___	**52** vermelho___	**77** azul___	**102** verde___
3 vermelho ___	**28** vermelho___	**53** vermelho___	**78** vermelho___	**103** azul___
4 verde ___	**29** azul___	**54** azul___	**79** verde___	**104** verde___
5 azul ___	**30** verde___	**55** vermelho___	**80** vermelho___	**105** vermelho___
6 vermelho___	**31**azul___	**56** verde___	**81** azul___	**106** azul___
7 verde___	**32** verde___	**57** azul___	**82** vermelho___	**107** verde___
8 vermelho___	**33** vermelho___	**58** azul___	**83** verde___	**108** vermelho___
9 azul___	**34** azul___	**59** verde___	**84** azul___	**109** verde___
10 vermelho___	**35** verde___	**60** vermelho___	**85** azul___	**110** azul___
11 verde ___	**36** vermelho___	**61** vermelho___	**86** verde___	**111** vermelho___
12 azul___	**37** verde___	**62** verde___	**87** verde___	**112** verde___
13 azul___	**38** azul___	**63** azul___	**88** vermelho___	**113** azul___
14 verde___	**39** vermelho___	**64** vermelho___	**89** vermelho___	**114** vermelho___
15 verde___	**40** verde___	**65** azul___	**90** azul___	**115** verde___
16 vermelho___	**41** azul___	**66** verde___	**91** vermelho___	**116** vermelho___
17 vermelho___	**42** vermelho___	**67** azul___	**92** verde___	**117** azul___
18 azul___	**43** verde___	**68** verde___	**93** azul___	**118** vermelho___
19 vermelho___	**44** vermelho___	**69** vermelho___	**94** azul___	**119** verde___
20 verde___	**45** azul___	**70** azul___	**95** verde___	**120** azul___
21 azul___	**46** vermelho___	**71** verde____	**96** vermelho___	**121** azul___
22 azul___	**47** verde___	**72** vermelho___	**97** vermelho___	**122** verde___
23 verde___	**48** azul___	**73** verde___	**98** verde___	**123** verde___
24 vermelho___	**49** azul___	**74** azul___	**99** azul___	**124** vermelho___
25 vermelho___	**50** verde___	**75** vermelho___	**100** vermelho___	**125** vermelho___

Total de Respostas: _____ Incorrectas ☒: _____ Correctas ✔ **:** _____

Folha de Registo

Teste Stroop: cor

Identificação/Código:_____ Data de avaliação: __/__/__

Instruções: Nesta parte vou-lhe pedir que me diga quais são as cores de cada um dos grupos de X's que aparecem nesta página. Vou-lhe pedir que faça isto primeiro para a 1ª coluna e avance depois para as seguintes à medida que for terminando. Só começa depois de eu dar o sinal (dizer "Pode começar"). Entendido? Atenção: Pode começar!

Tempo: Dê o sinal de partida ao mesmo tempo que aciona o cronómetro. O tempo limite é de 45 segundos.

Cotação: Marcar com um visto ✔ as respostas corretas, com uma cruz ☒ as respostas incorretas e com um **C** as correções espontâneas.

1 Vermelho ___	**21** Vermelho ___	**41** Azul ___	**61** Verde ___	**81** Azul ___
2 Azul ___	**22** Azul ___	**42** Verde ___	**62** Vermelho ___	**82** Verde ___
3 Verde ___	**23** Vermelho ___	**43** Azul ___	**63** Azul ___	**83** Vermelho ___
4 Vermelho ___	**24** Verde ___	**44** Vermelho ___	**64** Vermelho ___	**84** Azul ___
5 Azul ___	**25** Azul ___	**45** Verde ___	**65** Verde ___	**85** Verde ___
6 Vermelho ___	**26** Verde ___	**46** Azul ___	**66** Vermelho ___	**86** Azul ___
7 Verde ___	**27** Vermelho ___	**47** Verde ___	**67** Verde ___	**87** Verde ___
8 Azul ___	**28** Azul ___	**48** Vermelho ___	**68** Azul ___	**88** Vermelho ___
9 Vermelho ___	**29** Vermelho ___	**49** Azul ___	**69** Verde ___	**89** Verde ___
10 Verde ___	**30** Azul ___	**50** Verde ___	**70** Azul ___	**90** Azul ___
11 Azul ___	**31** Verde ___	**51** Vermelho ___	**71** Vermelho ___	**91** Vermelho ___
12 Verde ___	**32** Azul ___	**52** Verde ___	**72** Azul ___	**92** Azul ___
13 Azul ___	**33** Vermelho ___	**53** Azul ___	**73** Vermelho ___	**93** Vermelho ___
14 Vermelho ___	**34** Verde ___	**54** Vermelho ___	**74** Verde ___	**94** Verde ___
15 Verde ___	**35** Azul ___	**55** Verde ___	**75** Azul ___	**95** Vermelho ___
16 Azul ___	**36** Vermelho ___	**56** Vermelho ___	**76** Verde ___	**96** Verde ___
17 Vermelho ___	**37** Verde ___	**57** Azul ___	**77** Vermelho ___	**97** Azul ___
18 Verde ___	**38** Azul ___	**58** Vermelho ___	**78** Verde ___	**98** Verde ___
19 Azul ___	**39** Vermelho ___	**59** Verde ___	**79** Azul ___	**99** Vermelho ___
20 Vermelho ___	**40** Verde ___	**60** Azul ___	**80** Vermelho ___	**100** Azul ___

Total de Respostas: _____ Incorrectas ☒: _____ Correctas ✔ **:** _____

Folha de Registo

Teste Stroop: Cor/Palavra

Identificação/Código:_____ Data de avaliação: __/__/__

Instruções: Agora vamos fazer uma tarefa diferente. Queria que me dissesse a cor da tinta em que estão escritas as palavras, o mais depressa que puder. Comece no início da 1ª coluna, quando acabar passe à 2ª e assim sucessivamente. Se se enganar, corrija e continue. Só começa depois de eu dar o sinal (dizer "Pode começar"). Entendido? Atenção: Pode começar!

Tempo: Dê o sinal de partida ao mesmo tempo que aciona o cronómetro. O tempo limite é de 45 segundos.

Cotação: Marcar com um visto ✔ as respostas corretas, com uma cruz ☒ as respostas incorretas e com um **C** as correções espontâneas.

1 Azul ___	**26** Vermelho___	**51** Vermelho___	**76** Vermelho___	**101** Vermelho___
2 Verde ___	**27** Verde___	**52** Azul___	**77** Vermelho___	**102** Azul___
3 Azul ___	**28** Azul___	**53** Verde___	**78** Verde___	**103** Vermelho __
4 Vermelho ___	**29** Vermelho___	**54** Vermelho___	**79** Azul___	**104** Vermelho___
5 Vermelho ___	**30** Azul___	**55** Azul___	**80** Azul___	**105** Azul___
6 Verde___	**31** Vermelho___	**56** Vermelho___	**81** Vermelho___	**106** Verde___
7 Azul___	**32** Vermelho___	**57** Vermelho___	**82** Verde___	**107** Azul___
8 Azul___	**33** Azul___	**58** Verde___	**83** Vermelho___	**108** Verde___
9 Vermelho___	**34** Verde___	**59** Azul___	**84** Verde___	**109** Azul___
10 Verde___	**35** Azul___	**60** Verde___	**85** Verde___	**110** Verde___
11 Vermelho ___	**36** Verde___	**61** Verde___	**86** Azul___	**111** Azul___
12 Verde___	**37** Azul___	**62** Vermelho___	**87** Vermelho___	**112** Vermelho___
13 Verde___	**38** Verde___	**63** Verde___	**88** Azul___	**113** Vermelho___
14 Azul___	**39** Azul___	**64** Azul___	**89** Verde___	**114** Verde___
15 Vermelho___	**40** Vermelho___	**65** Vermelho___	**90** Vermelho___	**115** Azul___
16 Azul___	**41** Vermelho___	**66** Azul___	**91** Azul___	**116** Azul___
17 Verde___	**42** Verde___	**67** Vermelho___	**92** Vermelho___	**117** Vermelho___
18 Vermelho___	**43** Azul___	**68** Vermelho___	**93** Vermelho___	**118** Azul___
19 Azul___	**44** Azul___	**69** Azul___	**94** Verde___	**119** Vermelho___
20 Vermelho___	**45** Vermelho___	**70** Verde___	**95** Azul___	**120** Verde___
21 Vermelho___	**46** Verde___	**71** Azul____	**96** Verde___	**121** Verde___
22 Verde___	**47** Vermelho___	**72** Verde___	**97** Verde___	**122** Azul___
23 Azul___	**48** Verde___	**73** Azul___	**98** Vermelho___	**123** Vermelho___
24 Verde___	**49** Verde___	**74** Verde___	**99** Verde___	**124** Azul___
25 Verde___	**50** Azul___	**75** Azul___	**100** Azul___	**125** Verde___

Total de Respostas: _____ Incorrectas ☒: _____ Correctas ✔ : _____

Código - Tarefa de Codificação

1	2	3	4	5	6	7	8	9
—	⊥	⊐	L	⊔	○	Λ	×	=

Itens Exemplo

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

7	1	8	2	9	3	6	7	2	8	5	2	3	1	4	8	4	2	7	6

Memória de Digitos – SENTIDO DIRECTO					
Interrupção: Interromper após insucesso de **dois ensaios** de um mesmo item. Codificação de todas as respostas apresentadas entre 0 e 1.					
Cotação: **Por ensaio:** 0 ou 1 ponto por cada repetição incorrecta ou correcta, respectivamente **Por item:** ensaio 1 + ensaio 2					
	Sequência		**Cotação**		
Item1	Ensaio 1	1 – 7	0	1	
	Ensaio 2	6 – 3	0	1	
Item 2	Ensaio 1	5 – 8 – 2	0	1	
	Ensaio 2	6 – 9 – 4	0	1	
Item3	Ensaio 1	6 – 4 – 3 – 9	0	1	
	Ensaio 2	7 – 2 – 8 – 6	0	1	
Item 4	Ensaio 1	4 – 2 – 7 – 3 – 1	0	1	
	Ensaio 2	7 – 5 – 8 – 3 – 6	0	1	
Item 5	Ensaio 1	6 – 1 – 9 – 4 – 7 – 3	0	1	
	Ensaio 2	3 – 9 – 2 – 4 – 8 – 7	0	1	
Item 6	Ensaio 1	5 – 9 – 1 – 7 – 4 – 2- 8	0	1	
	Ensaio 2	4 – 1 – 7 – 9 – 3 – 8 – 6	0	1	
Item 7	Ensaio 1	5 – 8 – 1 – 9 – 2 – 6 – 4 – 7	0	1	
	Ensaio 2	3 – 8 – 2 – 9 – 5 – 2 – 7 – 4	0	1	
Item 8	Ensaio 1	2 – 7 – 5 – 8 – 6 – 2 – 5 – 8 – 4	0	1	
	Ensaio 2	7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8	0	1	
Forward Total Score (range 0 – 16)					

Memória de Digitos – SENTIIDO INVERSO						
	Sequência		Resposta	Cotação		
Item1	Ensaio 1	2 – 4		0	1	
	Ensaio 2	5 – 7		0	1	
Item 2	Ensaio 1	6 – 2 – 9		0	1	
	Ensaio 2	4 – 1 – 5		0	1	
Item3	Ensaio 1	3 – 2 – 7 – 9		0	1	
	Ensaio 2	4 – 9 – 6 – 8		0	1	
Item 4	Ensaio 1	1 – 5 – 2 – 8 – 6		0	1	
	Ensaio 2	6 – 1 – 8 – 4 – 3		0	1	
Item 5	Ensaio 1	5 – 3 – 9 – 4 – 1 – 8		0	1	
	Ensaio 2	7 – 2 – 4 – 8 – 5 – 6		0	1	
Item 6	Ensaio 1	8 – 1 – 2 – 9 – 3 – 6 – 5		0	1	
	Ensaio 2	4 – 7 – 3 – 9 – 1 – 2 – 8		0	1	
Item 7	Ensaio 1	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8		0	1	
	Ensaio 2	7 – 2 – 8 – 1 – 9 – 6 – 5 – 3		0	1	
Backward Total Score (range 0 – 14)						
Total Scorre (range 0 – 30)						

Iniciais do doente | | | | Data | | | | | | |
Dia Mês Ano

TESTE DE MEMÓRIA SELECTIVA

IMPRESSO 1

	1	2	3	4	5	6
rio						
silêncio						
casa						
carne						
pedra						
terra						
lago						
livro						
janela						
prazer						
vida						
conceito						

							TOTAIS
INTRUSÕES							
LTS							
CLTR							

IMPRESSO 2

	1	2	3	4	5	6
rua						
célula						
aldeia						
vestido						
motor						
bar						
material						
júri						
festa						
fábrica						
exército						
mãe						

							TOTAIS
INTRUSÕES							
LTS							
CLTR							