Is there evidence for resting-state EEG interhemispheric imbalance in people with depression? A pilot study

Isadora Valente

UMinho | 2023

Universidade do Minho
Escola de Psicologia

Isadora Maria Santos Valente

Is there evidence for resting-state EEG interhemispheric imbalance in people with depression? A pilot study

Jan 2023

Universidade do Minho
Escola de Psicologia

Isadora Maria Santos Valente

Is there evidence for resting-state EEG interhemispheric imbalance in people with depression? A pilot study

Dissertação de Mestrado

Mestrado em psicologia Aplicada

Trabalho efetuado sob a orientação
da Professora Doutora Sandra Carvalho
e do Professor Doutor Diego Pinal

Janeiro de 2023

Despacho RT - 31 /2019 - Anexo 3

Declaração a incluir na Tese de Doutoramento (ou equivalente) ou no trabalho de Mestrado

DIREITOS DE AUTOR E CONDIÇÕES DE UTILIZAÇÃO DO TRABALHO POR TERCEIROS

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

Atribuição-NãoComercial
CC BY-NC

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

[Esta licença permite que outros remisturem, adaptem e criem a partir do seu trabalho para fins não comerciais, e embora os novos trabalhos tenham de lhe atribuir o devido crédito e não possam ser usados para fins comerciais, eles não têm de licenciar esses trabalhos derivados ao abrigo dos mesmos termos.]

Agradecimentos

Primeiramente, gostaria de agradecer à minha orientadora, Dra. Sandra Carvalho, por todo o apoio e suporte que me providenciou ao longo deste projeto e pelos seus valiosos contributos que me inspiraram a querer aprender mais sobre esta área.

Igualmente, gostaria de agradecer ao meu co-orientador, Dr. Diego Pinal, pela orientação e acompanhamento extraordinário que me providenciou ao longo deste ano, fundamental para a execução deste projeto e para o meu processo de aprendizagem.

Gostaria igualmente de reconhecer e agradecer o apoio incansável da minha colega de equipa, Catarina Gomes, pela sua imensa disponibilidade e suporte ao longo desta dissertação.

Gostaria de deixar um agradecimento aos meus amigos por todo o inestimável suporte e carinho, que foi fundamental no decorrer desta jornada.

E finalmente, deixo um profundo agradecimento à minha família, pelo suporte incondicional ao longo do toda a minha jornada académica, aos quais eu devo a oportunidade privilegiada de poder seguir o meu percurso académico e profissional ambicionado.

DECLARAÇÃO DE INTEGRIDADE

Declaro ter atuado com integridade na elaboração do presente trabalho académico e confirmo que não recorri à prática de plágio nem a qualquer forma de utilização indevida ou falsificação de informações ou resultados em nenhuma das etapas conducente à sua elaboração.

Mais declaro que conheço e que respeitei o Código de Conduta Ética da Universidade do Minho.

Resumo

A perturbação Depressiva Major (PDM), é notória pela sua alta comorbilidade com perturbações de ansiedade (PA). Assimetrias de alfa frontal (AAF) e de alfa parietal (AAP) em Eletroencefalograma (EEG), tem sido propostas como um potenciais marcadores de PDM e de PA. No entanto, nem todos os estudos reportaram a evidência neste sentido, sendo necessária mais investigação para testar esta hipótese.

Neste estudo piloto examinamos AAF e AAP em EEG em estado de repouso em indivíduos com sintomatologia depressiva e ansiosa. Principais objetivos foram investigar se (1) indivíduos com sintomatologia depressiva diferem de indivíduos assintomáticos nos padrões de AAF e AAP; (2) se indivíduos com ansiedade comórbida apresentavam esses mesmos padrões.

Embora não tenham sido encontradas diferenças entre AAF e AAP entre os grupos deprimidos e de assintomáticos, poder de alfa frontal à esquerda e poder de alfa parietal à direita foram encontrados em todos os grupos. A ansiedade comórbida não aparentou influenciar os padrões de assimetria encontrados nos grupos. Este estudo não corroborou AAF e AAP como marcadores capazes de diferenciar indivíduos com base na sua sintomatologia depressiva ou ansiosa. Estudos futuros deverão explorar estas hipóteses em amostras maiores.

Palavras-Chave: Assimetria de alfa frontal, Assimetria de alfa parietal, Ansiedade Comórbida, Depressão major, EEG.

Abstract

Major depressive disorder (MDD) is notoriously highly comorbid with anxiety disorders (AD). Electroencephalography (EEG) resting-state frontal alpha (FAA) and parietal alpha asymmetry (PAA) have been proposed to be a potential marker of MDD and AD. However, not all studies have found evidence for this and, further investingation is needed to test this alpha asymmetry hypothesis.

In this pilot study, we examined resting-state EEG FAA and PAA in individuals experiencing depressive and anxious symptomology. The main aims were to investigate if (1) individuals with depressive symptoms differ from asymptomatic individuals in FAA and PAA patterns;(2) if individuals with comorbid anxiety showed these same patterns.

Although we did not find FAA and PAA between depressive and asymptomatic groups, a left-sided FAA and right-sided PAA were found across all groups. Comorbid anxiety did not seem to influence the asymmetry patterns found among these groups. This study did not support FAA and PAA as markers able to differentiate individuals based on depressive or anxious symptomology. Future studies should explore these hypotheses in larger samples.

Keywords: Comorbid Anxiety, EEG, Frontal Alpha Asymmetry, Major Depressive Disorder, Parietal Alpha Asymmetry.

Contents

Background 10
Major Depressive disorder prevalence and impact 10
MDD issues and treatment difficulties 10
Neurobiology of Depression 11
Electroencephalography 12
Frontal Alpha Asymmetry 12
Parietal Alpha Asymmetry 14
Study aims 14
Methods 15
Sample 15
Experimental procedure 16
Instruments 17
EEG Recording Procedure 18
EEG Data Processing 18
Statistical analysis 19
Results 20
FAA differences between depressed and asymptomatic individuals 20
FAA differences between Comorbid and Anxious individuals 22
PAA differences between Depressed and Asymptomatic individuals 24
PAA differences between Comorbid and Anxious individuals 26
Discussion 27
Frontal alpha asymmetries 27
Anxiety influence in FAA 28
Parietal alpha asymmetries 29
Anxiety influence on PAA 30
Limitations 30
Bibliography 32
Approval declaration by the ethics committee 39

Tables

Table 1. Demographics of depressed and asymptomatic participants..... 16
Table 2. Demographics of Comorbid and Anxious participants..... 17
Table 3. Differences between groups for age, gender and Beck Anxiety Inventory Scale..... 21
Table 4. Variables correlation with Interhemispheric asymmetry 21
Table 5. Differences in FAA and PAA between participants with/without depressive symptomology 23

Figures

Figure 1 Linear graphs for Depressed and Asymptomatic groups examining FAA 22
Figure 2 Linear graphs for Comorbid and Anxious groups examining FAA 24
Figure 3 Linear graphs for Depressed and Asymptomatic groups examining PAA 25
Figure 4 Linear graphs for Comorbid and Anxious groups examining PAA 26

Background

Major Depressive disorder prevalence and impact

Major depressive disorder (MDD) is one of the most prevalent mental health disorders and the leading cause of incapacitation. It is estimated that around 280 million people were dealing with depression in 2019, an estimated 3.76% of the worldwide population (Global Health Data Exchange, 2022)[1]. In Portugal it is estimated that approximately 5.88% of the population may be experiencing a depressive disorder, affecting 7.39% of women and 4.16% male. Furthermore, between 45% to 51% of people with MDD are estimated to have at least one comorbid anxiety disorder (Kessler et al., 2015). These patients frequently experience poorer treatment responses, as comorbidity is associated with more severe symptomatology, increased suicidal ideation and attempts, and increased rates of relapse (Ionescu et al., 2013).

MDD is characterized by distinct changes in neurovegetative, cognitive, and affective functions (American Psychiatric Association, 2013; Greer et al., 2012), which can substantially impair individuals' ability to function and cope across multiple contexts (e.g., work, social life, and overall daily life). MDD requires at least five symptoms to be present on most days for a minimal period of two weeks, with at least depressed mood or anhedonia as core features (APA, 2022). Its symptoms may include persistent sadness, loss of interest and pleasure, feelings of guilt, low self-worth, disturbances in sleep, appetite and libido, difficulties concentrating accompanied by psychomotor alterations, and ultimately may lead to suicidal ideation or attempt.

MDD issues and treatment difficulties

Although MDD is generally diagnosed on a symptoms-based approach (APA, 2022), this is a complex multidimensional disorder showing widespread neurobiological dysfunction (Pitsillou et al., 2020; Strawbridge et al., 2017). Underlying biological factors that sustain one depressive syndrome may vary significantly among individuals with the same diagnosis (Fonseka et al., 2018; Spellman & Liston, 2020). Up to 30% of patients still experience clinical symptomatology after treatment (Rush et al., 2006). This elicits the need for a deeper understanding of this disorder's underlying mechanisms to develop tailored interventions, personalized towards patients' needs (Ionescu et al., 2013; Spellman & Liston, 2020).

[1] The Institute for Health Metrics and Evaluation (2019). Global Burden of Disease. Global Health Data Exchange. Retrieved June 2, 2022, from https://vizhub.healthdata.org/gbd

Neurobiology of Depression

Evidence stemming from neuroimaging studies has shown dysregulation over the dorsolateral prefrontal cortex (DLPFC) in MDD, displaying left hypoactivation and right hyperactivation (e.g., Grimm et al., 2008). Neuromodulation studies using tDCS and TMS targeting bilateral DLPFC in order to balance interhemispheric metabolic function by increasing and/or inhibiting cortical excitability, have been able to significantly reduce depressive symptomatology; highlighting the frontal asymmetry association with depressive status (e.g., Bennabi & Haffen, 2018; Jog et al., 2019; Rizvi & Khan, 2019; Siddiqi et al., 2020). It is thought that DLPFC's ability to exert top-down control trough reappraisal and suppression strategies over negative affect arising from hyperactive limbic structures (e.g. the amygdala) could be compromised in individuals with MDD (Koenigs & Grafman, 2009; Williams, 2017). Furthermore, this asymmetry has been proposed to reflect the differential activation of two affective motivational systems (i.e. approach/withdrawal model; Allen et al., 2004; Davidson et al., 1993), which could reflect a dispositional tendency towards experiencing increased negative affect. Succinctly, hyperactive right DLPFC has been associated with a tendency to experience predominantly negative affect (e.g. sadness, fear, disgust), behavioural inhibition, hypervigilance and withdrawal tendencies, while a hypoactive left PFC reflects decreased approach tendencies, associated with motor retardation, anhedonia, and decreased tendency to engage with pleasant stimuli (Jesulola et al., 2015; Sutton & Davidson, 2016).

Additionally, metabolic alterations in the parietal lobes (PL) have been reported in MDD. In contrast to DLPFC, hypoactivation over the right, relative to the left has been associated with depressive disorders in resting conditions (Gonçalves et al., 2006; Lin et al., 2021; Shen et al., 2021; Zhang et al., 2018). The right PL has been associated with the modulation of autonomic arousal in emotional states (Heller et al., 2010). Hence, hypoactivation has been associated with depressive states whereas, inversely, hyperactivation has been linked to increased arousal states (e.g. anxiety). PLs are thought to have an important role in supporting cognitive and affective processes; and their abnormal functioning also been associated with deficits in the regulation of affect capabilities (Chen et al., 2013; R. H. Kaiser et al., 2015).

Further, the DLPFC and the PLs are connected through the frontoparietal network (FPN). Functional connectivity within the FPN has been observed to be decreased in depressed individuals (Schultz et al., 2019; Wei et al., 2014). This network is important for the optimal modulation of emotional processing and cognitive control (e.g. Dosenbach et al., 2008; Grieder et al., 2020; Spellman & Liston, 2020; Zhang et al., 2018; Zwenetworkerings et al., 2019). Therefore, these asymmetric patterns of

activation seen in the frontal and parietal regions can reflect dysregulation over a broader system. In that regard, their anatomical accessibility (i.e. surface cortical regions) makes them particularly suitable targets for neuromodulation interventions (e.g. TMS, tDCS), potentially permitting the modulation of broader neuronal network communication.

Electroencephalography

Electroencephalography (EEG) research has contributed significantly to the understanding of markers of abnormal activity in MDD. EEG it is a non-invasive neuroimaging modality able to record the ongoing activity of the brain, by detecting post-synaptic activity from large populations of neurons firing synchronously (Buskila et al., 2019). Due to its high affordability and portability compared to other neuroimaging modalities (e.g. MRI, PET), EEG is particularly advantageous to use in a clinical setting as a tool for identifying markers of brain activity of potential psychopathological processes, in real time.

Alpha oscillatory activity (8 – 12Hz) seems to provide an index of neuronal activity in cortical regions, being inversely correlated with metabolic activity (Laufs et al., 2003). More specifically, greater alpha power (i.e., defined by increased alpha amplitude) correlates with hypometabolic activity, inversely, lower alpha power correlates with hypermetabolic activity (Bruder et al., 2017; Coan & Allen, 2004).

Research has broadly documented alpha interhemispheric asymmetry within the DLPFC and PLs in depressed individuals(Allen & Reznik, 2015; Henriques & Davidson, 1991; Koller-Schlaud et al., 2020; Palmiero & Piccardi, 2017; Stewart et al., 2011; van der Vinne et al., 2017). In particular, the frontal regions have received the bulk of attention within asymmetry literature, known as frontal alpha asymmetry (FAA).

Frontal Alpha Asymmetry

FAA in depressed individuals is typically displayed by greater alpha power towards the left PFC relative to the right contralateral side, as observed in resting conditions as well as during tasks-eliciting frontal activation (e.g. Allen & Reznik, 2015; de Aguiar Neto & Rosa, 2019; Gordon et al., 2010; Stewart et al., 2014; Thibodeau et al., 2006). To define FAA patterns in this study, great alpha power over the left frontal hemisphere relative to the right contralateral site will be described as left-side FAA, while the inverse will be described as right-sided FAA.

Most literature suggests that depressive patients tend to display greater left-sided FAA compared to healthy controls (Debener, Beauducel, Nessler, Brocke, Heilemann, & Kayser, 2000; A. K. Kaiser et al., 2018; Stewart et al., 2014). Many of those studies showed promising evidence that left-sided FAA

was able to distinguish those currently depressed from euthymic individuals (e.g. Foong Lee et al., 2017; Koo et al., 2019) and even to differentiate individuals with a previous history of depression from those never depressed (de Aguiar Neto & Rosa, 2019; Smith et al., 2017; Thibodeau et al., 2006). Furthermore, left-side FAA has been associated with negative affect, predicting mood deterioration (Papousek et al., 2014) and the occurrence of depressive symptoms (Mitchell & Pössel, 2012).

Nevertheless, the literature on FAA has been somewhat heterogeneous (e.g Quinn et al., 2014), as some authors did not find differences between depressed individuals and healthy controls (e.g. Arns et al., 2016; van der Vinne et al., 2017). Moreover, a metanalysis by Van der Vinne et al., (2017) investigated the diagnostic value of FAA in a large cross-sectional data; concluding that it was not a reliable diagnostic biomarker for MDD due to small non-significant effect size and high heterogeneity across studies. Besides, some studies with clinically depressed samples have reported the inverse pattern, displayed by right-sided FAA (e.g. Jesulola et al., 2016).

Overall, FAA has also been proposed as a potential marker of vulnerability/risk to develop affective disorders (Allen & Reznik, 2015; Goodman et al., 2021), showing to be relatively stable across time (Allen et al., 2003; van der Vinne et al., 2017; Towers & Allen, 2009). Heterogeneity across studies is thought to be due to high methodological variability and a lack of standardized methods (Stewart et al., 2010, 2014). It might also be a reflection of the intrinsic complexity of the psychopathological mechanisms implicated in MDD, reflecting intrasubject variability (e.g. de Kovel et al., 2019). Thus, few studies have properly explored the role of comorbid anxiety in FAA which may partly contribute to the heterogeneity observed in interhemispheric asymmetry studies (Drysdale et al., 2017; van der Vinne et al., 2017).

Various studies have reported leftward FAA in anxiety disorders (e.g. Blackhart et al., 2006; Briesemeister et al., 2013; Davidson et al., 2000; Lewis et al.; Mennella et al., 2017), although FAA patterns have been quite heterogeneous among these. For instance, certain types of anxiety (e.g., social anxiety, obsessive disorder, apprehension, generalized anxiety) have been associated with a rightward FAA trend (Al-Ezzi et al., 2020, Smith, Zambrano-Vazquez, & Allen, 2016). When looking at anxious comorbidity in depressed samples, the FAA relationship becomes less clear. Mathersul et al., (2008) reported that although anxious individuals displayed greater left-sided FAA, depressed individuals with comorbid anxiety showed symmetrical frontal activity. Other studies did not find FAA differences between comorbid and healthy individuals (e.g. A. K. Kaiser, Doppelmayr, et al., 2018; Lin et al., 2021). Despite an apparent FAA's relation with anxiety, the literature on comorbid anxiety is still scares and inconclusive.

Parietal Alpha Asymmetry

Alpha asymmetry in the PLs has been documented in MDD, although it has received comparably less attention in research. Even so, evidence suggests that parietal alpha asymmetries (PAA) could hold value as a neurobiological marker for depression (e.g. Grin-Yatsenko et al., 2010; Koller-Schlaud et al., 2020). Most PAA literature points to depressed individuals presenting decreased right parietal activation relative to the contralateral lobe, i.e., right-sided PAA when compared to non-ill controls (Bruder et al., 2007; Henriques & Davidson, 1990; Koller-Schlaud et al., 2020; Volf & Passynkova, 2002). Similarly, to FAA, resting-state PAA has been proposed to be a potential marker of vulnerability to psychopathology (Bruder et al., 2012; Henriques & Davidson, 1990; Stewart et al., 2011), having shown moderate long-term reliability (Bruder et al., 2005, 2012; Koller-Schlaud et al., 2020). However, some studies found inconclusive results linking PAA as a marker of active depressive status (e.g. Debener et al., 2000; Henriques & Davidson, 1991).

Studies investigating PAA in comorbid individuals have been heterogeneous and inconclusive.

Kentgen et al., (2000) reported right-sided PAA in female adolescents with MDD without comorbid anxiety, compared to the control group, although the comorbid MDD group showed no PAA, suggesting that anxious symptomatology may reduce the perceived asymmetry over the PL. Similarly, another studied did not encountered PAA differences between healthy controls and patients with comorbid MDD (Lin et al., 2021). Conversely, Bruder et al. (1997) found depressed comorbids showed left-sided PAA, which suggested increased activation over the right PL. In general, anxiety has been mostly associated with increased activation over the right parietal region,i.e., left-sided PAA (Heller & Nitschke, 1997; Grieder et al.,2020). Left-sided PAA has been observed in individuals with social anxiety (e.g. Davidson et al., 2000) and PTSD (e.g., Metzger et al., 2004). Overall, evidence suggests that depressive disorders tend to relate to hypoactivation in the right PL relative to the left PL, while anxiety seems to be inversely associated with hyperactivation at the same region. This may diffuse the perceived PAA among comorbid individuals.

Study aims

Resting-state FAA and PAA has been proposed as putative markers of affective dysfunction. However, not all studies have found evidence for this potential marker and further studies are needed to test this alpha asymmetry hypothesis.

The primary objective of this study was to examine resting-state FAA and PAA in individuals experiencing depressive symptomology. It was hypothesized that (1) depressed individuals would display greater left-sided FAA, compared to asymptomatic individuals; (2) Depressed individuals would display

greater right—sided PAA compared to asymptomatic individuals.

The second aim of this study was to examine anxiety's influence on resting-state FAA and PAA. Explorative analyses were run between comorbid and anxious individuals to assess if anxiety would influence interhemispheric patters in comorbid samples. No hypotheses were stated due to a lack of studies assessing comorbidity and due to the high heterogeneity across results.

Methods

Forty-one participants were recruited through advertising on social media, flyers at clinical spaces (e.g., Associação de Psicologia da Universidade do Minho) at the University of Minho, and through the credit Platform SONORA providing course credits for participation in experimental studies. The EEG data were collected at the Psychological Neuroscience Laboratory of the University of Minho, after approval by the local ethics committee (SECVS 174/2017). Recruitment took place in 2019 (n = 13) and 2020 (n = 16).

Sample

Participants included in the study were (1) aged between 18 and 30 years, (2) able to provide signed consent, and (3) able to complete self-report questionnaires. A total of 12 participants were excluded from the sample. Participants were excluded if: (1) had other significant or unstable neurological or psychiatric disorders besides depressive and/or anxiety disorders; (2) a diagnosis of personality disorder or any serious or life-threatening medical conditions; (3) were taking psychiatric medication (4) or were taking illicit substances. Two participants were removed from the data due to EEG recording defects, leaving a final sample of 29 participants (24 females; age M = 20.8; SD =1.9).

Accepted volunteers were organized in different groups based on cut-off scores defined for the clinical level of depressive and/or anxious symptomatology assessed by the *Beck Depression Inventory–II* (BDI; Beck et al., 1961) and the *Beck Anxiety Inventory* (BAI; Quintão et al., 2013). The instruments description can be found in the instrument section.

To answer the primary question of this study, participants were initially organized into two groups

Table 1

Demographics of depressed and asymptomatic participants

	Asymptomatic (*n= 18*)		Currently Depressed (*n*=11)	
Variables		**Range**		**Range**
Age (M ±SD)	20.8 ±2.4	18 - 27	21.8 ±2.9	18 - 28
Sex, n(%)				
Female	15 (83.34)	-	9 (81.82)	-
Male	3 (16.67)	-	2 (18.2)	-
Years of education	13.59 ± 1.9	9 - 17	14.2 ±1.7	12 - 16
BDI-II (M±SD)	3.7 ± 2.7	0 - 9	19.3 ± 9.9	10 - 45
BAI -II (M±SD)	11.9 ± 7.7	1 - 31	19.5 ±10.1	2 - 43

Note: Education level data was missing for three participants of the total sample; Years of education data was missing for three participants of the total sample.

(see table 1): the *depressed* group (*n* = 11; 9 females; age *M* = 21.6; *SD* =1.9) experiencing depressive symptomatology (BDI scores ≥ 10), and an *Asymptomatic* group (*n* = 18; 15 females; age *M* = 20.3; *SD* = 1.7) free from depressive symptomatology (BDI scores <10). To explore the influence of anxiety over the dependent variable (i.e., interhemispheric alpha power), in a second analysis participants were re-organized into a *Comorbid* group (*n* = 10; 9 females; age *M* = 21.6; *SD* = 1.9), with clinical levels of depressive and anxiety symptomatology (BDI scores ≥ 10 and BAI scores ≥ 8) and an *Anxious* group (*n* = 13; 11 females; age *M* = 20.3; *SD* =2), including participants that had clinical anxiety but no clinical depressive symptomatology (BAI scores ≥ 8 and BDI scores <10) (see table 2).

Experimental procedure

All data collection took place at the Psychological Neuroscience Laboratory at the University of Minho, in Portugal. Participants were initially briefed on the study protocol and provided with any clarification regarding safety and data collection concerns. Following the signature of the informed consent, all volunteers were asked to complete a questionnaire collecting: demographic data, medication status, use of illicit substances and clinical information. Participants were then asked to complete self-report psychometric instruments followed by the EEG recording, with each session taking approximately 40 minutes.

Table 2

Demographics of Comorbid and Anxious participants

	Comorbid (*n= 10*)		Anxious (*n=13*)	
Variables		**Range**		**Range**
Age, years (*M ±SD*)	21.2 ± 2.1)	18 – 24	20.7 ±2.6)	18 – 27
Sex, *n*(%)				
Female	9 (90)	-	11(84.62)	-
Male	1 (10)	-	2 (15.4)	-
Years of education (*M ±SD*)	14.5 ±1.6	12 – 16	13.5 ± 2.1	9 - 17
BDI-II (*M±SD*)	20.1 ±10.1	10 – 45	4.5 ±2.6	0 - 9
BAI -II (*M ±SD*)	21.3±8.8	12 - 43	15 ±6.8	7 - 31

Note: Education level data was missing for three participants of the total sample; Years of education data was missing for two participants of the total sample.

Instruments

Beck Depression Inventory-II

Participants completed the validated Portuguese version (Campos & Gonçalves, 2011) of the Beck Depression Inventory-II (BDI; Beck et al., 1961). This inventory is composed of 21 self-report items measuring characteristics, attitudes, and symptoms of depression. It assesses the presence and severity of depressive symptomatology. Total inventory score ranges from 0 to 63 with higher scores indicating higher depressive symptomatology. Item scores range between 0 to 3, organized by the frequency in which respondents experienced reported symptoms, ranging from affective, cognitive, and somatic complaints (irritability, hopelessness, sleep, concentration) during the last week. BDI has shown high internal consistency, with a Cronbach's alpha of .86 being among the most widely used methods to classify depression (Beck et al., 1961).

Beck Anxiety Inventory

Participants completed the Portuguese version of *Beck Anxiety Inventory* (BAI; Quintão et al., 2013); to determine the presence and severity of anxiety. This inventory is composed of 21 - self-repot items scored from 0 to 3, organized by the frequency of the symptoms (e.g., agitation, fear, nervousness) experienced during the last week. The total score ranges from 0 to 63, scaling anxiety in terms of severity.

The original instrument has proven high internal consistency (α = .92) and acceptable test-retest reliability over a week, r (81) = .75 (Beck, Steer, et al., 1988). The validated Portuguese version holds good psychometric properties as a unidimensional measure, with a good model fit person reliability (.79) and high item reliability (.99). Hence, it has shown good specificity quality, providing less overlap between symptoms of depression and anxiety (Beck, Epstein, et al., 1988).

EEG Recording Procedure

Participants were comfortably seated and instructed to stay still, relaxed, and to avoid excessive blinking and movement when possible. Data was recorded in continuous mode and indications were given verbally to participants to when to open or to close their eyes. A portable 20-channel low-density EEG cap was used due to its quick applicability and easy portability, making it appropriate for clinical settings. The resting-state EEG recordings lasted about 18 minutes in total, divided in alternative blocks of 3 mins for each condition: eyes-open (EO) and eyes closed (EC). Block were presented in one of two counterbalanced orders (EO EC EO EC EO EC or EC EO EC EO EC EO). The recording resulted in a total of 9 minutes of EEG data, per condition. A 20-channel Starstim (Neuroelectric, Barcelona, Spain) device was used, with electrodes placed following the 10/20 international system (Jasper, 1958). Electrooculogram (EOG) was recorded from two bipolar channels and impedances were kept below 5 kΩ. Data was collected using a 500Hz of continuous digitalization rate, with a bandpass filter of 0.001 – 100 Hz. The electrodes covering the scalp included frontal (Fp1, Fp2, F3, F4, F7, F8, Fz), central (C3, C4, Cz) temporal (T7, T8), parietal (P3, P4, P7, P8, Pz), and occipital (O1, O2, Oz) sites. The analyzed frequency band was defined within the alpha (8–13 Hz) range.

EEG Data Processing

Stored EEG data was preprocessed in MATLAB R2021b, using the EEGlab toolbox (Delorme & Makeig, 2004). All channels were then bandpass filtered (0.5 to 45 Hz) using a 4th- order phase- shift free Butterworth filter. Data were visually inspected for major artifacts compromising all channels and rejection data periods was applied when necessary, removing 1.7% of the total data at this stage. Next, followed automated detection and elimination of electrodes with low correlation ($r \leq 0.8$) with neighbouring electrodes and of electrodes with a flat signal lasting longer than 5 seconds. Then, correction of large transient artifacts in the data was performed using artifact subspace reconstruction via Clean Raw Data EEGlab plugin. Independent Component Analysis (ICA) was performed and IC label EEGlab plugin (Pion-Tonachini et al., 2019) used to aid in the inspection of the resulting independent components.

Components with a 20% or lower probability of containing brain activity, and a residual variance superior to 20%, were removed from data reconstruction. Further, visual inspection of the spectrum frequency density was made to determine signal quality and channels were removed if they significantly deviated from expected normal spectral power (e.g., power distribution following 1/f law). All removed channels were then interpolated. Then, preprocessed data was segmented into 2-second non-overlapping epochs, whereas segments containing artifacts were removed if they had: (1) values of ±100μV; (2) contained trends with slopes exceeding 75μV*;* (3) improbable data points or abnormal distributions with a single channel limit of 5 SDs; (4) spectral power in frequencies from 0 to 2 Hz outside the range from 50 to -50 dB, or outside the range 25 to -100 dB from frequencies between 20 and 40 Hz.

Finally, data for participants with a minimum of 30 artifact-free data epochs (i.e., 1 min) was used for power spectral density (PSD) calculations using the p-welch function from the Signal Processing Toolbox, in MATLAB, through Welch's overlapped segment averaging estimator using a Hamming window. Afterward, the eight power values (0.5 Hz resolution) in the alpha frequency band (8–12 Hz) were extracted and averaged for each analyzed electrode (i.e., F3, F4, F7, F8; P3, P4; P7, P8), separately. Averaged alpha power values were then transformed by calculating their natural logarithm. FAA and PAA were calculated using the laterality quoficient (LQ; Reznik & Allen, 2018) function: ln (right electrode) – ln(left electrode), which enables calculation of an interhemispheric asymmetry index based on the difference between homologs electrodes [e.g. ln(F4) – ln(F3)].

Statistical analysis

All calculations were conducted in IBM SPSS Statistics Inc. 28.0 Software. For the missing data treatment, an analysis of the data matrix was run, indicating a total of 0.74% of missing values across the BAI and BDI observations. Little's missing completely at Random Test (MCAR) demonstrated that this data was missing in a random way (χ^2 = 156.23; *df* =159, *p* =.547); hence an Expected Maximization Analysis procedure as implemented in SPSS was run to estimate missing values.

In order to reduce the effect of extreme values in the analysis, individual scores deviating from the analysed variables mean (i.e, BDI, BAI, Alpha PSD at each electrode) at least 2.2 times the interquartile range were considered univariate outliers (Hoaglin et al., 1986; Hoaglin & Iglewicz, 1987) and were winsorized before the statistical analysis (Tukey, 1962).

For statistical tests, the alpha level was kept at $\alpha \leq 0.05$. To examine between groups differences, a series of independent sample t-tests were run to assess BAI scores and age; while a chi-square test for

gender differences (see table 3). Additionally, to investigate gender, age, BAI and BDI scores influence on the dependent variables (e.g. FAA and PAA scores) for each condition, a Pearson's correlation was run for age, BAI, and BDI scores, and a point-biserial correlation test was run for gender (see table 4). Depressed and asymptomatic groups differ significantly in BAI scores, $t(27) = -2.22$, $p = 0.35$, therefore, these scores were used as a covariate in ANCOVA analysis for these groups. Additionally, a marginal significance was observed between the Anxious and Comorbid group, $t(27) = -1.92$, $p = .068$, whereas Comorbid group showed slightly increased levels of anxiety. No other confounding variables were found to influence the data.

To examine interhemispheric asymmetry, a series of two-way mixed repeated measures ANCOVAs were run for all electrodes pairs (i.e., F3/F4; F7/F8; P3/P4; P7/P8), with the between-subjects factor Group (i.e., depressed vs asymptomatic) and the within-factor as Hemisphere (i.e., right versus left electrode) tested independently for each condition (i.e., EC and EO). To explore the influence of anxiety on interhemispheric asymmetries, two-way mixed repeated measures ANOVA were run for the same electrode pairs, with the between-subjects factor Group (i.e., comorbid versus anxious) and the within-factor Hemisphere (i.e., right versus left homologous electrode), tested independently for each condition (i.e., EC and EO).

Results

FAA differences between depressed and asymptomatic individuals

To analyse alpha lateralization over frontal hemispheres at both pairs of electrodes (F3/F4 and F7/F8), two-way mixed repeated measure ANCOVAs were performed with Group as the between-subjects factor and hemisphere as a within-subjects factor. A main effect of factor Hemisphere was found at the F3/F4 sites, showing greater alpha power over the left (F3) compared to the right (F4) hemisphere in both EC, $F(1, 26) = 41.888$, $p < .001$, $\eta^2 = .617$, and EO conditions, $F(1, 26) = 63.882$, $p < .001$, $\eta^2 = .711$, irrespective of depressive status. No main effect of Group factor was found (EC: $F(1, 26) = .419$, $p = .523$; EO: $F(1, 26) = .067$, $p = .797$). There was no statistically significant interaction between Group and Hemisphere factor for frontal alpha power (EC: $F(1, 26) = .262$, $p = .613$; EO: $F(1, 26) = .536$, $p = .471$; see figure 1).

Table 3

Differences between groups for age, gender and Beck Anxiety Inventory Scale

	Age		BAI		Gender	
	t	*p*	*t*	*p*	χ^2	*p*
Depressed vs Asymthomatic	-1.05	.303	-2.22	**.0.35****	.011	.920
Comorbid vs Anxious	.42	.677	1.92	**.068***	.144	.704

**Statistically significant, p <.05

*Marginally significant

Table 4

Variables correlation with Interhemispheric asymmetry

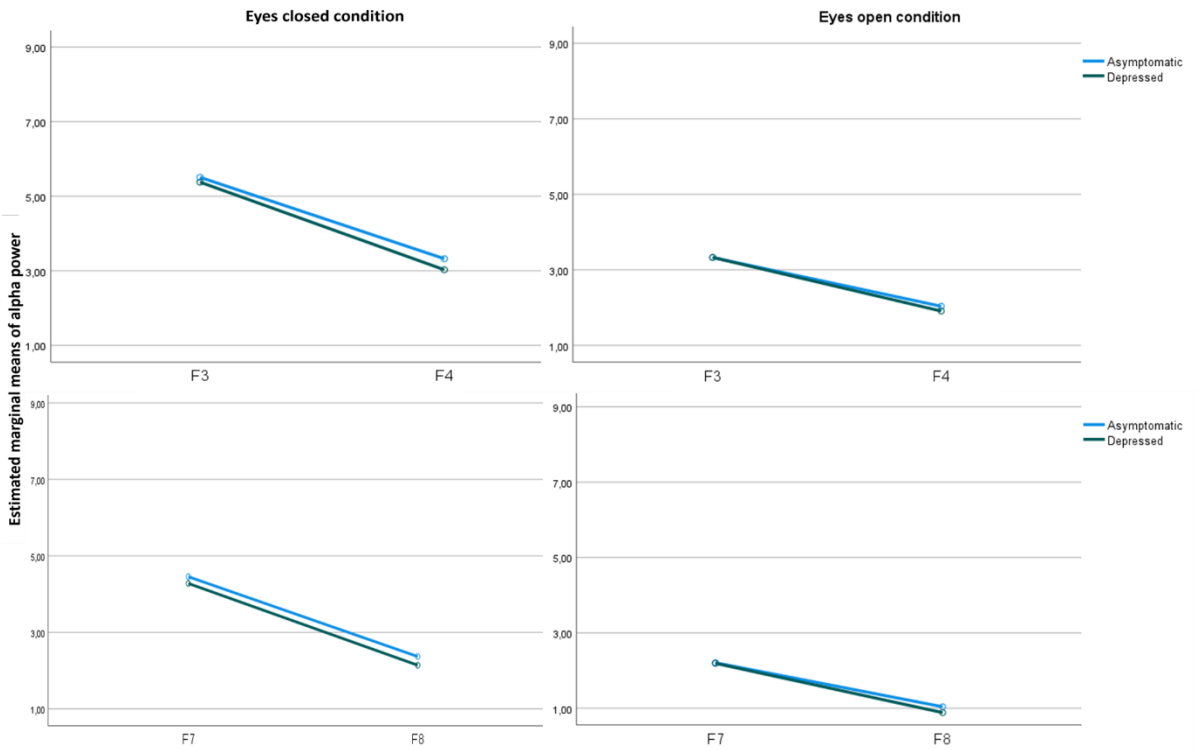
LQ electrodes	Condition	Age		BAI		BDI		Gender	
		r	*p*	*r*	*p*	*r*	*p*	*rpb*	*p*
F3/F4	EC	.041	.835	-.056	.772	-.079	.684	.109	.572
	EO	-.027	.890	.057	.770	-.039	.840	-.054	.781
F7/F8	EC	.020	.919	-.038	.846	-.194	.314	.158	.412
	EO	-.004	.983	.012	.953	-.328	**.082***	.024	.903
P3/P4	EC	-.121	.538	.126	.516	.010	.958	.073	.709
	EO	-.055	.782	.310	.101	.287	.131	-.188	.328
P7/P8	EC	.130	.508	.064	.742	.277	.146	.204	.288
	EO	.054	.783	.131	.498	.185	.336	-.047	.807

*Marginally significant

F7/F8 electrodes pair analysis followed the same trend, showing a main effect of factor Hemisphere in both conditions (EC, $F(1, 26) = 44.969, p<.001, \eta^2$=-634; EO, $F(1, 26) = 41.557, p<.001, \eta^2$=.615), with greater alpha power over the left (F7) relative to the right (F8) side. No main effect of Group factor was found for EO, $F(1, 26) = .227, p = .638$, neither for EC, $F(1, 26) = .524, p = .476$, condition. Furthermore, no interaction effects were found between Group and Hemisphere factor in either

Figure 1

Mixed repeated measures ANCOVA linear graph for Depressed and Asymptomatic groups examining FAA



Note. Four mixed repeated measures ANCOVA linear graphs for Depressed and Asymptomatic groups, showing estimated means of alpha power values (at Y axis) at F3/F4 and F7/F8 pair of electrodes (at X axis), for both EC and EO conditions.

condition (EC: F(1, 26) = .032,p= .859; EO: F(1, 26) = .501,p= .485; see figure 1).

Notwithstanding, exploratory analyses performed outside the main analysis, detected a potential lateralization effect at F7/F8 electrodes (see table 5). An independent-sample t-tests detected a marginally significant difference between depressed and asymptomatic groups in EO condition, t(27)= 1.934, p = 0.64, suggesting an increased tendency for left-sided asymmetry in the depressed group (M = -.908, SD = .21), compared to the asymptomatic group (M = -.755, SD =.20) for when the eyes are open. Although ANCOVA did not corroborated this lateralization effect, these tests suggest potential alpha power trend over F7 site in depressed individuals.

FAA differences between Comorbid and Anxious individuals

Only a small portion of the asymptomatic group participants reported not experiencing clinical levels of anxiety (n = 5). Thus, the mean BAI score for this group was within the mild range

Table 5

Differences in FAA and PAA between participants with and without depressive symptomology

		Asymptomatic (*n* = 18)		Depressed (*n=11*)		t-test	
Frontal Alpha Asymmetry		*M*	*SD*	*M*	*SD*	*t*	*p*
F3/F4	EC	-.51	.15	-.57	.13	1.11	.28
	EO	-.5	.15	-.56	.14	1.01	.32
F7/F8	EC	-.63	.14	.-.68	.1	.98	.33
	EO	-.76	.2	-.91	.21	1.93	**.06***
Parietal Alpha Asymetry							
P3/P4	EC	.7	.21	.71	.13	-.05	.96
	EO	.28	.19	.32	.19	-.55	.59
P7/P8	EC	1.06	.4	1.23	.63	-.91	.37
	EC	.53	.19	.56	.23	-.38	.71

Note. Sample t-tests were run to assess differences between of FAA and PAA values at difference set of electrodes, between depressed and asymptomatic groups. *p* - value < .05

*Marginally significant

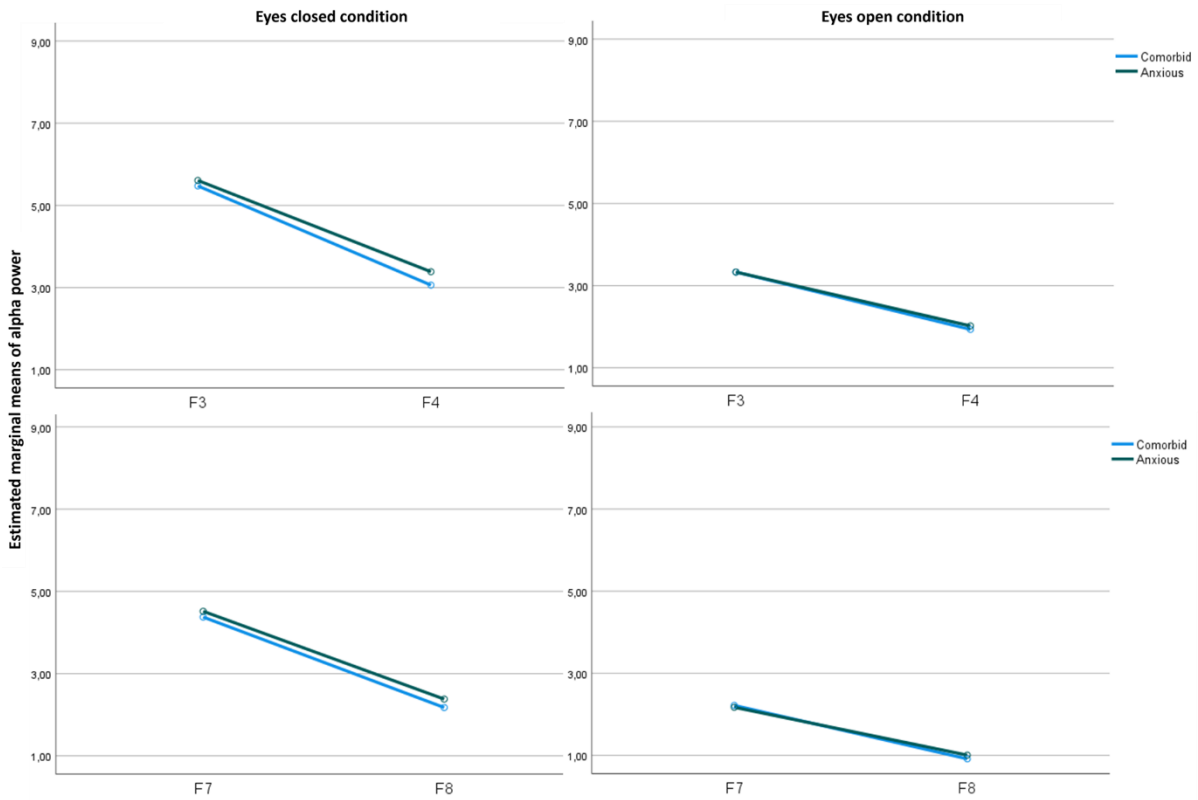
(M=11.94, SD=7.7). To test for anxiety influence in FAA, tests were run contrasting individuals scoring at the clinical range of both BDI and BAI symptomatology (i.e., Comorbid group, n =10) and individuals scoring at clinical range in BAI (i.e., Anxious group, *n* =13).

A two-way mixed ANOVA showed a main effect of Hemisphere factor for the F3/F4 pair, showing greater alpha power over the left hemisphere in both EC, $F(1, 21) = 191.096$, $p < .001$, $\eta^2 = .901$, and EO conditions, $F(1, 21) = 241.213$, $p < .001$ $\eta^2 = .92$. However, no differences in alpha power distribution were found among the anxious and comorbid individuals in either EC, $F(1, 21) = .409$, $p = .529$, or EO conditions, $F(1, 21) = .034$, $p = .856$. Also, no statistically significant interaction was found between Groups and Hemisphere factors (EC, $F(1, 21) = .573$, $p = .015$; EO, $F(1, 21) = .246$, $p = .625$; see figure 2).

A second two-way mixed ANOVA showed a main effect of Hemisphere factor for the F7/F8 pair, showing greater alpha power over the left hemisphere in both EC, $F(1, 21) = 184.43$, $p < .001$, $\eta^2 = .898$., and EO conditions, $F(1, 21) = 150.008$, $p < .001$, $\eta^2 = .877$. However, no differences in alpha power

Figure 2

Mixed repeated measures ANOVA linear graph for Comorbid and Anxious groups examining FAA



Note. Four mixed repeated measures ANOVA linear graphs for Comorbid and Anxious groups, showing estimated means of alpha power values (at Y axis) at F3/F4 and F7/F8 pair of electrodes (at X axis), for both EC and EO conditions.

distribution were found between the anxious and comorbid groups in either EC, $F(1, 21) = .323$, $p = .576$, or EO conditions, $F(1, 21) = .016$, $p = .900$. Also, no statistically significant interaction was found between Group and Hemisphere factors (EC, $F(1, 21) = .040$, $p = .843$; EO $F(1, 21) = .478$, $p = .497$; see figure 2).

PAA differences between Depressed and Asymptomatic individuals

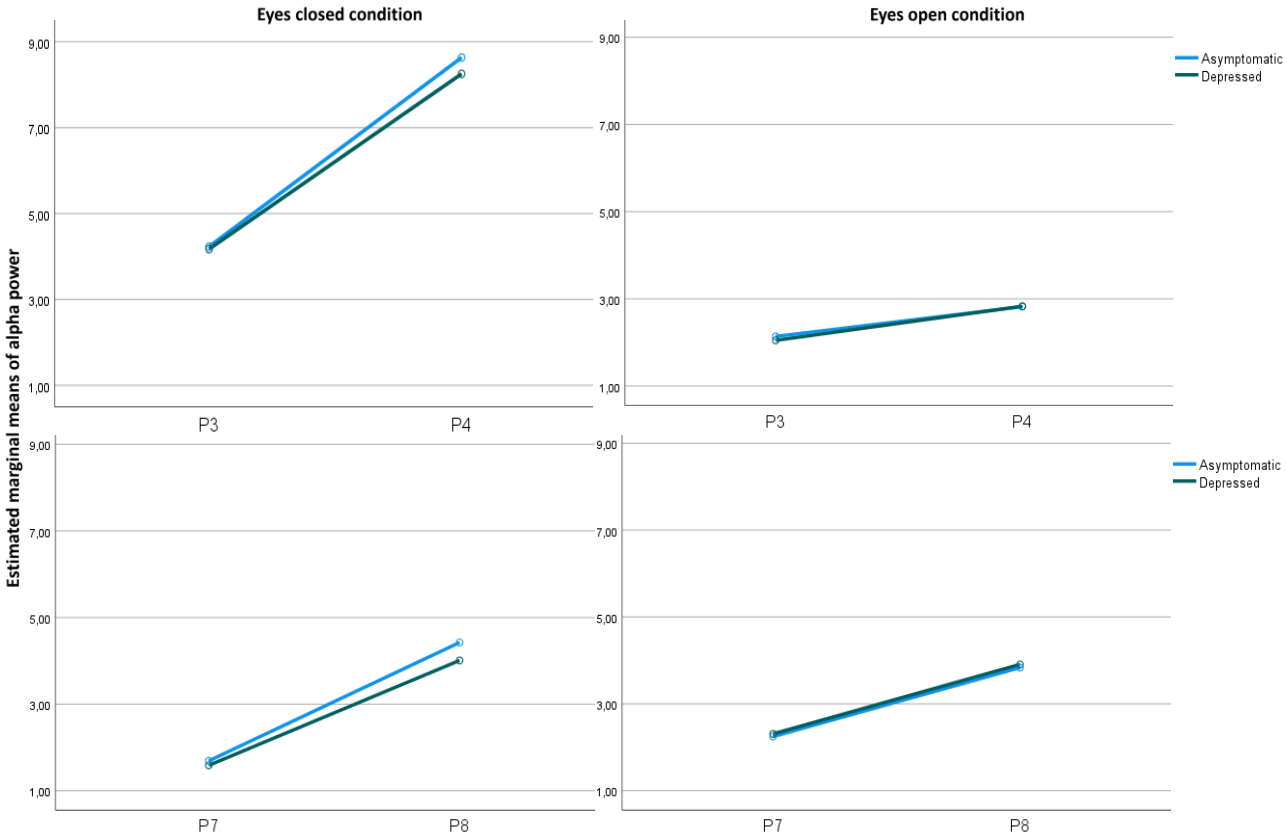
A two-way mixed ANCOVA showed a main effect for the factor Hemisphere (at P3/P4 electrodes) in the EC condition $F(1, 26) = 42.490$, $p < .001$, $\eta^2 = .620$,showing greater alpha power over the right hemisphere. However, for the EO condition $F(1, 26) = 2.22$, $p < .148$ no main effect was found for the factor Hemisphere. Additionally, no main effects of Group were found (EC: $F(1, 26) = .204$, $p = .655$; EO: $F(1, 26) = .0.13$, $p = .909$). No interaction effect was found between Group and Hemisphere factors

on parietal alpha power in any condition (EC, $F(1, 26) = .345$, $p = .562$; E0, $F(1, 26) = .153$, $p = .699$; see figure 3) .

For the P7/P8 electrodes pair, a two-way mixed ANCOVA showed a main effect for the factor Hemisphere in the EC condition $F(1, 26) = 35.436$, $p < .001$, $\eta^2 = .577$, showing greater alpha power over the right hemisphere. However, for the EO condition, $F(1, 26) = 30.28$, $p < .001$, no main effect was found for the factor Hemisphere. Also no main effects of Group were found in neither condition, EC: $F(1, 26) = .203$, p= .656; EO: $F(1, 26) = .41$, $p = 842$. No interaction effect was found between Group and Hemisphere on parietal alpha power in any condition (EC, $F(1, 26) = .515$, $p = .480$; E0, $F(1, 26) = .002$, $p = .966$; see figure 3).

Figure 3

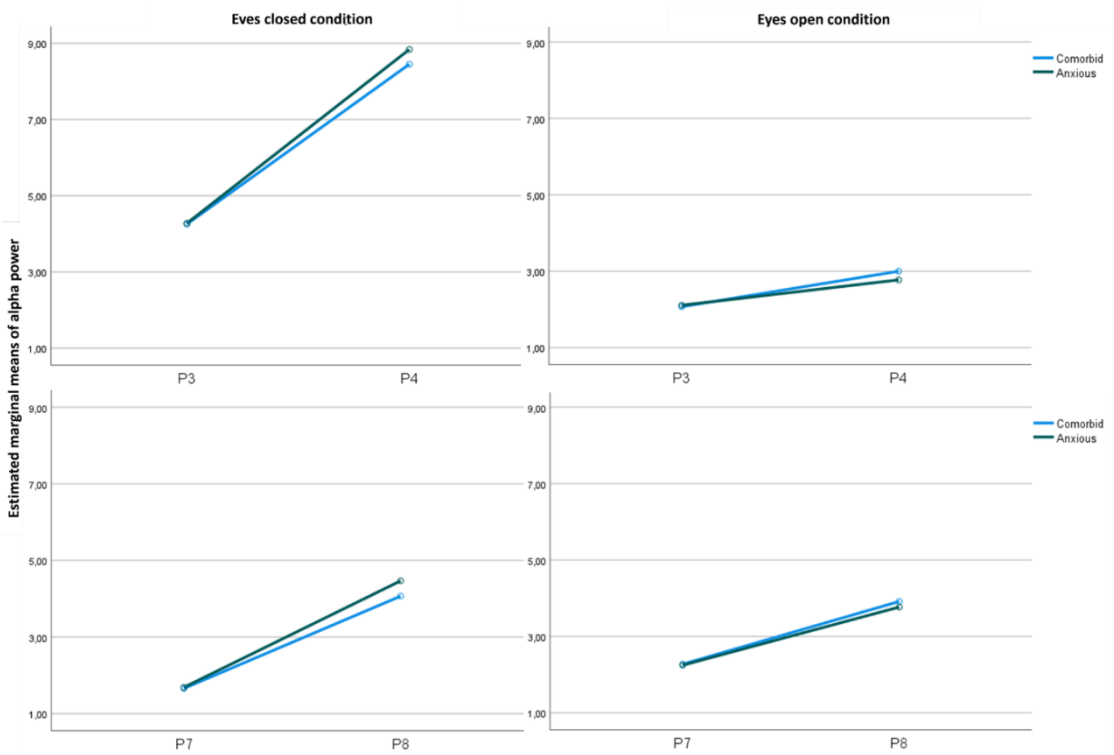
Mixed repeated measures ANCOVA linear graph for Depressed and Asymptomatic groups examining PAA



Note. Four mixed repeated measures ANCOVA linear graphs for Depressed and Asymptomatic groups, showing estimated means of alpha power values (at Y axis) at P3/P4 and P7/P8 pair of electrodes (at X axis), for both EC and EO conditions.

Figure 4

Mixed repeated measures ANOVA linear graph for Comorbid and Anxious groups examining PAA



Note. Four mixed repeated measures ANOVA linear graphs for Comorbid and Anxious groups, showing estimated means of alpha power values (at Y axis) at P3/P4 and P7/P8 pair of electrodes (at X axis), for both EC and EO conditions.

PAA differences between Comorbid and Anxious individuals

To explore the influence of anxiety in PAA, two-way mixed ANOVAs were run to investigate alpha lateralization between comorbid and anxious individuals. A main effect of Hemisphere factor emerged in the analysis of the P3/P4 electrodes pair for both conditions, EC: F (1, 21) = 311.301, p < .001, η^2 =.937 and EO, F (1, 21) = 30.206, p <.001 η^2 =.59, showing greater alpha power over the right (P4), relative to the left (P3) hemisphere. No main effect of Group emerged for either condition, EC, F (1, 21) = .157, p = .696; EO, F (1, 21) = .076, p = .785. Furthermore, no statistically significant interaction was found between Hemisphere and group, EC, F(1, 21) = .542, p = .47; EO, F(1, 22) = .833 p = .372 (see figure 4).

For the P7/P8 electrodes pair, a main effect of Hemisphere factor emerged for both EC, F(1, 21) = 137.937, p < .001, η^2 =.868 and EO conditions, F (1, 21) = 157.599, p < .001, η^2 =.882, showing greater alpha power over the right (P8), relative to the left (P7) hemisphere. No main effect emerged for the Group factor in either condition, EC, F (1, 21) = .133, p = .719; EO, F (1, 21) = .227, p < .639.

Furthermore, no statistically significant interaction was found between Group and Hemisphere: EC, F (1, 21) = .709, p = .409; EO, F(1, 21) = ..227 p = 639 (see figure 4).

Discussion

The present study investigated bilateral EEG resting-state alpha power over frontal and parietal regions. We aimed to investigate FAA and PAA viability as a putative EEG marker in individuals with clinical levels of depressive symptomatology and comorbid anxiety.

As a main objective, we examined if depressive individuals would differ in FAA and PAA patterns from the asymptomatic ones. Contrary to our prediction, no FAA and PAA differences were found between these groups, although a main effect emerged showing a leftward FAA trend and rightward PAA trend in both groups. As a second objective, comorbid anxiety influence on FAA and PAA patterns were examined by comparing individuals experiencing both depressive and anxious symptomatology (i.e., Comorbid group) with individuals experiencing only clinical anxiety (i.e., Anxious group). Results suggested that anxiety did not influence interhemispheric asymmetries in these individuals, as no FAA and PAA differences were found between these groups.

Frontal alpha asymmetries

The first hypothesis underlying the main objective predicted that depressed individuals would display greater left-sided FAA over frontal electrodes sites compared to the asymptomatic group. No differences were found between these groups. Other studies have also failed to report differences between depressed and the control groups (e.g. Mathersul et al., 2008; Szumska et al., 2021; Tenke, 2000).

However, a main effect emerged showing that both groups displayed increased left-sided FAA. As left-side FAA has been associated with depressive disorders (Coan & Allen, 2004; Debener et al., 2000; Koo et al., 2019; Stewart et al., 2014), the encountered pattern in the depressed group seems to be in line with major literature (e.g. Koo et al., 2019). However, and contrary to our prediction, the asymptomatic group did not differ from the depressed group, also showing the same left-sided FAA.

However, this leftward FAA trend might reveal that, inadvertently, this group could be mostly composed by participants with a particular dispositional profile, remitted individuals, and/or at risk of developing affective disorders. Some studies have reported left-sided FAA in euthymic individuals with a previous history of MDD (de Aguiar Neto & Rosa, 2019; Smith et al., 2017; Stewart et al., 2014),. For instance, Nusslock et al., (2011) showed that left-side FAA in young adults was able to predict the later onset of depression; thus, FAA has also been reported in infants of depressed mothers (Goodman et al.,

2021), supporting evidence of its trait/phenotypical properties. Furthermore, left-sided FAA in healthy individuals has been also observed to relate with increased neuroticism scores (Farahi et al., 2019), and increasing evidence is leaning toward resting-state FAA trait/dispositional characteristics . Moreover, in line with the approach/withdrawal motivational model prepositions (Coan & Allen, 2004; Davidson et al., 1993), this pattern could reflect a dispositional affective tendency. Considering this theory, left sided FAA would reflect a tendency to predominantly engage in withdrawal and avoidant responses, while conversely, display lower approach and motivational tendencies. This activation imbalance has also been related to increase predisposition to develop depressive symptomatology (Stewart et al., 2014; Sutton & Davidson, 2016).

Overall, these results would seemly challenge FAA viability as a marker for depression. This would be in in line with growing literature questioning it's reliability as a state-depend marker of psychopathology (e.g. Allen & Reznik, 2015; Towers & Allen, 2009; van der Vinne et al., 2017).

Notwithstanding, an unexpected noteworthy finding, emerged from exploratory analysis as an independent sample t-tests showed a marginally significant difference over F7/F8 electrode pairs only for the EO condition. The depressed group seemingly displayed greater left-sided FAA compared to the asymptomatic (see table 5). This is a surprising result, since most of literature reported left-sided FAA over F4/F3 pair of electrodes (Thibodeau et al., 2006; van der Vinne et al., 2017), but very few reported a lateralization effect exclusively at F7/F8 electrodes pairs. This might also be due to most studies focusing mostly on F3/F4 electrodes, as many don't include other frontal electrodes in their analysis. Metzen et al., (2022) and Ocklenburg et al., (2019) found asymmetry differences at F7/F8 but not at F3/F4 electrodes, although this was in healthy individuals. Additionally, we found a marginally significant correlation between F8/F7 electrode pairs in the EO condition with BDI scores (see table 4). These results at EO condition are particularly unexpected since research as shown EC condition to be more sensitive to detect effects since alpha activity is known to synchronize in response to eyes closing (Barry et al., 2007). Nonetheless, these results were not supported by ANCOVA analysis since it did not detect group's difference at any level. It's unknown what might be the underlying cause of these results.

Anxiety influence in FAA

Under the second objective of this study, it was examined if FAA patterns differ between the Comorbid and the Anxious group. No FAA differences were found between these groups, although a main effect emerged with both groups displaying left-sided FAA. Leftward FAA has been mostly associated with anxious arousal, panic and phobic disorders (Heller, 1993; Nusslock et al., 2015; Smith et al., 2016).

Nonetheless, since this study did not account for the type of anxiety, it is unknown if this sample could be experiencing a more predominant form of arousal-based anxiety. However, this would seem unlikely, since other forms of anxiety that have been associated with the opposing FAA pattern (i.e., right-sided FAA), exist frequently in depressive and anxious samples. It is the case for generalized anxiety, one of the most comorbid disorders with depression, and apprehension anxiety (i.e. worry), commonly found across depressed and anxious individuals (e.g. social anxiety, obsessive disorder; Fingelkurts & Fingelkurts, 2015; Mathersul et al., 2008; Smith et al., 2016).

Thus, the lack of differences in FAA between the comorbid and anxious groups is surprising, as it suggests that depressive symptomatology it's not the explanatory variable of the observed FAA leftward trend. This was seemingly supported by the lack of overall significant correlation between BDI scores and FAA analysis (see table 4). Moreover, the correlation between BAI scores and FAA, also suggests that the left-sided FAA does not seem to reflect anxiety scores. This highlights that the active symptomatology assessed in this study does not seem properly explain the encountered FAA results, whereas other factors need to be accounted to interpret these data.

Parietal alpha asymmetries

Additionally, under the primary aim of this study, it was a hypothesised that the depressed group would display right-sided PAA compared to the asymptomatic group. Contrary to prediction, no PAA differences between groups emerged. Indeed, some studies did not find PAA asymmetries between depressed and healthy individuals (e.g. Debener et al., 2000; Henriques & Davidson, 1991).

Additionally, a main effect emerged with both groups displaying right-sided PAA, for the EC condition. Again, both depressed and asymptomatic groups displayed the PAA pattern often reported in depressed samples (e.g. Bruder et al., 2007; Henriques & Davidson, 1990; Koller-Schlaud et al., 2020; Volf & Passynkova, 2002), although statistical significance was only achieved in the EC. It's unclear the reason of lack of significance in the EO condition. However, PAA has been observed to be greater in EC conditions then during EO (e.g. Metzen et al.,2021).

These results, build upon the left-sided FAA results, showing that the overall sample (i.e. groups both with and without clinical depressive symptomology) seems to display the profile typically associated with depressive disorders (Bruder et al., 2017; Henriques & Davidson, 1990; Thibodeau et al., 2006). Right-sided PAA has also been observed in individuals with a history of MDD. Henriques & Davidson (1990) observed that remitted patients displayed greater rightward PAA compared to never-depressed individuals. Hence, PAA has shown endophenotype characteristics, being observed in the offspring of

depressed parents (Bruder et al., 2005) and in descendants of probands (Bruder et al., 2012). Therefore, this could reinforce that this study might have captured a group of individuals with remitted or with increased vulnerability to developing an affective disorder (e.g. Stewart et al., 2011), although this is only speculatory.

Anxiety influence on PAA

Additionally, anxiety influence was examined in PAA by comparing comorbid and anxious groups. No differences were found in PAA between these groups (e.g. Lin et al., 2021). However, both presented a main effect indicating greater right-sided PAA in both EO and EC. This is surprising, as both groups are clinically anxious, it could be expected an increase in activation over right PL due to increased levels of baseline arousal (Heller et al., 2010; Kemp et al., 2010; Bruder et al., 1997). In general, literature points toward a lack of asymmetry observed in posterior regions when anxiety is present in comorbid samples, as increased arousal over right PL is thought to mask the hypoactivity seen in depressive disorders (Mathersul et al., 2008). This would hypothetically suggest that these participants were presenting overall low levels of arousal (Heller et al., 2010), despite their self-reported anxiety. This would also seem to contradict the earlier left-sided FAA results, which have been mostly linked to arousal-based anxiety. This would again divert from the hypothesis that these asymmetries reliably reflect affective symptomology, whereas other factors might be underlying the patterns seen in this sample.

Limitations

To carefully consider these results, some limitations that need to be considered. The absence of a healthy group without any clinical symptomatology undermines the ability to examine true differences, since the asymmetries observed, could reflect the engagement of overlapping neurobiological systems related to active anxious and depressive symptomatology (Coan & Allen, 2004; Reznik & Allen, 2018). Furthermore, an underpowered sample may have limited the ability to detect true differences; additionally, unmatched groups and possible heterogeny among participant characteristics (e.g. handedness; subtype of depression; type of anxiety; past personal and familial psychiatric history) reduce the ability to see recognizable patterns associated with these asymmetries.

Another limitation was the lack of screening for past affective disorders or familial psychiatric history, which are known to be linked to FAA and PAA (e.g. Goodman et al., 2021; Hill et al., 2020).

Further, methodological limitations may also be influencing results, since studies have alerted for montages and electrode placement being a potential factor for heterogeneous results found in literature

(Ocklenburg et al., 2019; Stewart et al., 2014; van der Vinne et al., 2017).

Conclusion

The present study results did not support FAA and PAA evidence as markers able to differentiate individuals based on their clinical levels of 'depressive or anxious symptomatology.

In general, our results suggest that these interhemispheric asymmetries were not related to affective symptomology assessed in the sample. Since these asymmetries have not been exclusive to psychopathology, these results could reflect a group of individuals that display a particular profile, whereas this pattern could reflect trait-like characteristics (Farahi et al., 2019; Millis et al., 2022). Nonetheless, it could be interesting for future studies to examine if the encountered asymmetry patterns could also reflect the phenotypical risk for a subtype of anxious depression (Drysdale et al., 2017; Nusslock et al., 2015), whereas clinical anxiety might be a preceding symptom.

Future investigation exploring these hypotheses in larger samples may be able to provide a clearer picture of the factors underlying these asymmetries. Thus, it is important to further investigate the relation of putative trait, state and endophenotypic variables contribution for these asymmetries, and how do they predict psychopathological manifestation. Furthermore, studies using other frequency bands in relation to alpha frequencies might provide more precise markers of the mechanisms associated with depression and anxiety (e.g. Lin et al., 2021), as alpha oscillations in isolation, seem to be limited in their ability to be used as core diagnostic markers of psychopathology.

BIBLIOGRAPHY

Al-Ezzi, A., Selman, N. K., Faye, I., & Gunaseli, E. (2020). Electrocortical brain oscillations and social anxiety disorder: a pilot study of frontal alpha asymmetry and delta-beta correlation. *Journal of Physics: Conference Series*, *1529*(5), 052037. https://doi.org/10.1088/1742-6596/1529/5/052037

Allen, J. J. B., Coan, J. A., & Nazarian, M. (2004). Issues and assumptions on the road from raw signals to metrics of frontal EEG asymmetry in emotion. *Biological Psychology*, *67*(1–2), 183–218. https://doi.org/10.1016/J.BIOPSYCHO.2004.03.007

Allen, J. J. B., Keune, P. M., Schönenberg, M., & Nusslock, R. (2018). Frontal EEG alpha asymmetry and emotion: From neural underpinnings and methodological considerations to psychopathology and social cognition. *Psychophysiology*, *55*(1). https://doi.org/10.1111/PSYP.13028

Allen, J. J. B., & Reznik, S. J. (2015). Frontal EEG Asymmetry as a Promising Marker of Depression Vulnerability: Summary and Methodological Considerations. *Current Opinion in Psychology*, *4*, 93. https://doi.org/10.1016/J.COPSYC.2014.12.017

Allen, J. J. B., Urry, H. L., Hitt, S. K., & Coan, J. A. (2003). *The stability of resting frontal electroencephalographic asymmetry in depression*. https://doi.org/10.1111/j.1469-8986.2003.00149.x

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. https://doi.org/10.1176/APPI.BOOKS.9780890425596

Arns, M., Bruder, G., Hegerl, U., Spooner, C., Palmer, D. M., Etkin, A., Fallahpour, K., Gatt, J. M., Hirshberg, L., & Gordon, E. (2016). EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. *Clinical Neurophysiology*, *127*(1), 509–519. https://doi.org/10.1016/J.CLINPH.2015.05.032

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

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*(1), 77–100. https://doi.org/10.1016/0272-7358(88)90050-5

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, *4*(6), 561–571. https://doi.org/10.1001/ARCHPSYC.1961.01710120031004

Bennabi, D., & Haffen, E. (2018). Transcranial Direct Current Stimulation (tDCS): A Promising Treatment for Major Depressive Disorder? *Brain Sciences 2018, Vol. 8, Page 81*, *8*(5), 81. https://doi.org/10.3390/BRAINSCI8050081

Blackhart, G. C., Minnix, J. A., & Kline, J. P. (2006). Can EEG asymmetry patterns predict future development of anxiety and depression?: A preliminary study. *Biological Psychology*, *72*(1), 46–50. https://doi.org/10.1016/J.BIOPSYCHO.2005.06.010

Briesemeister, B. B., Tamm, S., Heine, A., & Jacobs, A. M. (2013). Approach the Good, Withdraw from the Bad—A Review on Frontal Alpha Asymmetry Measures in Applied Psychological Research. *Psychology*, *04*(03), 261–267. https://doi.org/10.4236/PSYCH.2013.43A039

Bruder, G. E., Bansal, R., Tenke, C. E., Liu, J., Hao, X., Warner, V., Peterson, B. S., & Weissman, M. M. (2012). Relationship of resting EEG with anatomical MRI measures in individuals at high and low risk for depression. *Human Brain Mapping*, *33*(6), 1325. https://doi.org/10.1002/HBM.21284

Bruder, G. E., Fong, R., Tenke, C. E., Leite, P., Towey, J. P., Stewart, J. E., McGrath, P. J., & Quitkin, F. M. (1997). Regional brain asymmetries in major depression with or without an anxiety disorder: A

quantitative electroencephalographic study. *Biological Psychiatry*, *41*(9), 939–948. https://doi.org/10.1016/S0006-3223(96)00260-0

Bruder, G. E., Stewart, J. W., & McGrath, P. J. (2017). Right brain, left brain in depressive disorders: Clinical and theoretical implications of behavioral, electrophysiological and neuroimaging findings. *Neuroscience & Biobehavioral Reviews*, *78*, 178–191. https://doi.org/10.1016/J.NEUBIOREV.2017.04.021

Bruder, G. E., Tenke, C. E., Warner, V., Nomura, Y., Grillon, C., Hille, J., Leite, P., & Weissman, M. M. (2005). Electroencephalographic measures of regional hemispheric activity in offspring at risk for depressive disorders. *Biological Psychiatry*, *57*(4), 328–335. https://doi.org/10.1016/J.BIOPSYCH.2004.11.015

Bruder, G. E., Tenke, C. E., Warner, V., & Weissman, M. M. (2007). Grandchildren at High and Low Risk for Depression Differ in EEG Measures of Regional Brain Asymmetry. *Biological Psychiatry*, *62*(11), 1317. https://doi.org/10.1016/J.BIOPSYCH.2006.12.006

Buskila, Y., Bellot-Saez, A., & Morley, J. W. (2019). Generating Brain Waves, the Power of Astrocytes. *Frontiers in Neuroscience*, *13*, 1125. https://doi.org/10.3389/FNINS.2019.01125

Chen, A. C., Oathes, D. J., Chang, C., Bradley, T., Zhou, Z. W., Williamsa, L. M., Glover, G. H., Deisseroth, K., & Etkin, A. (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(49), 19944–19949. https://doi.org/10.1073/PNAS.1311772110

Coan, J. A., & Allen, J. J. B. (2004). Frontal EEG asymmetry as a moderator and mediator of emotion. *Biological Psychology*, *67*(1–2), 7–50. https://doi.org/10.1016/j.biopsycho.2004.03.002

Davidson, R. J., Marshall, J. R., Tomarken, A. J., & Henriques, J. B. (2000). While a phobic waits: regional brain electrical and autonomic activity in social phobics during anticipation of public speaking. *Biological Psychiatry*, *47*(2), 85–95. https://doi.org/10.1016/S0006-3223(99)00222-x

de Aguiar Neto, F. S., & Rosa, J. L. G. (2019). Depression biomarkers using non-invasive EEG: A review. *Neuroscience & Biobehavioral Reviews*, *105*, 83–93. https://doi.org/10.1016/J.NEUBIOREV.2019.07.021

de Kovel, C. G. F., Aftanas, L., Aleman, A., Alexander-Bloch, A. F., Baune, B. T., Brack, I., Bülow, R., Filho, G. B., Carballedo, A., Connolly, C. G., Cullen, K. R., Dannlowski, U., Davey, C. G., Dima, D., Dohm, K., Erwin-Grabner, T., Frodl, T., Fu, C. H. Y., Hall, G. B., … Francks, C. (2019). No alterations of brain structural asymmetry in major depressive disorder: An ENIGMA consortium analysis. *American Journal of Psychiatry*, *176*(12), 1039–1049. https://doi.org/10.1176/APPI.AJP.2019.18101144

Debener, S., Beauducel, A., Nessler, D., Brocke, B., Heilemann, H., & Kayser, J. (2000). Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. *Neuropsychobiology*, *41*(1), 31–37. https://doi.org/10.1159/000026630

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*, 9–21. https://10.1016/j.jneumeth.2003.10.009

Drysdale, A. T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., Fetcho, R. N., Zebley, B., Oathes, D. J., Etkin, A., Schatzberg, A. F., Sudheimer, K., Keller, J., Mayberg, H. S., Gunning, F. M., Alexopoulos, G. S., Fox, M. D., Pascual-Leone, A., Voss, H. U., … Liston, C. (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine*, *23*(1), 28–38. https://doi.org/10.1038/NM.4246

Fingelkurts, A. A., & Fingelkurts, A. A. (2015). Altered Structure of Dynamic Electroencephalogram Oscillatory Pattern in Major Depression. *Biological Psychiatry*, *77*(12), 1050–1060. https://doi.org/10.1016/J.BIOPSYCH.2014.12.011

Fingelkurts, Al. A., & Fingelkurts, An. A. (2010). Short-Term EEG Spectral Pattern as a Single Event in EEG Phenomenology. *The Open Neuroimaging Journal*, *4*, 130. https://doi.org/10.2174/1874440001004010130

Foong Lee, P., Pei Xin Kan, D., Croarkin, P., Kar Phang, C., Doruk, D., & Abdul Rahman, T. (2017). Neurophysiological correlates of depressive symptoms in young adults: A quantitative EEG study. *Clinical Neuroscience, 47,* 315–322. https://doi.org/10.1016/j.jocn.2017.09.030

Gold, C., Fachner, J., & Erkkilä, J. (2013). Validity and reliability of electroencephalographic frontal alpha asymmetry and frontal midline theta as biomarkers for depression. *Scandinavian Journal of Psychology*, *54*(2), 118–126. https://doi.org/10.1111/SJOP.12022

Gonçalves, S. I., de Munck, J. C., Pouwels, P. J. W., Schoonhoven, R., Kuijer, J. P. A., Maurits, N. M., Hoogduin, J. M., van Someren, E. J. W., Heethaar, R. M., & Lopes Da Silva, F. H. (2006). Correlating the alpha rhythm to BOLD using simultaneous EEG/fMRI: Inter-subject variability. *NeuroImage*, *30*(1), 203–213. https://doi.org/10.1016/J.NEUROIMAGE.2005.09.062

Goodman, S. H., Liu, R., Lusby, C. M., Park, J. S., Bell, M. A., Newport, D. J., & Stowe, Z. N. (2021). Consistency of EEG asymmetry patterns in infants of depressed mothers. *Developmental Psychobiology*, *63*(4), 768–781. https://doi.org/10.1002/DEV.22046

Gordon, E., Palmer, D. M., & Cooper, N. (2010). EEG alpha asymmetry in schizophrenia, depression, PTSD, panic disorder, ADHD and conduct disorder. *Clinical EEG and Neuroscience*, *41*(4), 178–183. https://doi.org/10.1177/155005941004100404

Greer, T. L., Kurian, B. T., & Trivedi, M. H. (2012). Defining and Measuring Functional Recovery from Depression. *CNS Drugs 2010 24:4*, *24*(4), 267–284. https://doi.org/10.2165/11530230-000000000-00000

Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., Niehaus, L., Boeker, H., & Northoff, G. (2008). Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment: An fMRI Study in Severe Major Depressive Disorder. *Biological Psychiatry*, *63*(4), 369–376. https://doi.org/10.1016/J.BIOPSYCH.2007.05.033

Grin-Yatsenko, V. A., Baas, I., Ponomarev, V. A., & Kropotov, J. D. (2010). Independent component approach to the analysis of EEG recordings at early stages of depressive disorders. *Clinical Neurophysiology*, *121*(3), 281–289. https://doi.org/10.1016/J.CLINPH.2009.11.015

Harrewijn, A., van der Molen, M. J. W., & Westenberg, P. M. (2016). Putative EEG measures of social anxiety: Comparing frontal alpha asymmetry and delta–beta cross-frequency correlation. *Cognitive, Affective and Behavioral Neuroscience*, *16*(6), 1086–1098. https://doi.org/10.3758/S13415-016-0455-Y

Heller, W. (1993). Neuropsychological Mechanisms of Individual Differences in Emotion, Personality, and Arousal. *Neuropsychology*, *7*(4), 476–489. https://doi.org/10.1037/0894-4105.7.4.476

Heller, W., & Nitschke, J. B. (1997). Regional Brain Activity in Emotion: A Framework for Understanding Cognition in Depression. *Cognition and Emotion*, *11*(5–6), 637–661. https://doi.org/10.1080/026999397379845A

Heller, W., Nitschke, J. B., & Lindsay, D. L. (2010). Neuropsychological Correlates of Arousal in Self-reported Emotion, *11*(4), 383–402. https://doi.org/10.1080/026999397379854

Henriques, J. B., & Davidson, R. J. (1990). Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. *Journal of Abnormal Psychology*, *99*(1), 22–31. https://doi.org/10.1037//0021-843X.99.1.22

Henriques, J. B., & Davidson, R. J. (1991). Left frontal hypoactivation in depression. *Journal of Abnormal Psychology*, *100*(4), 535–545. https://doi.org/10.1037//0021-843X.100.4.535

Hill, K. E., Neo, W. S., Hernandez, A., Hamrick, L. R., Kelleher, B. L., & Foti, D. (2020). Intergenerational transmission of frontal alpha asymmetry among mother-infant dyads. *Biological*

Psychiatry. Cognitive Neuroscience and Neuroimaging, *5*(4), 420. https://doi.org/10.1016/J.BPSC.2019.12.003

Hoaglin, D. C., & Iglewicz, B. (1987). Fine-tuning some resistant rules for outlier labeling. *Journal of the American Statistical Association*, *82*(400), 1147–1149. https://doi.org/10.1080/01621459.1987.10478551

Hoaglin, D. C., Iglewicz, B., & Tukey, J. W. (1986). Performance of Some Resistant Rules for Outlier Labeling. *Journal of the American Statistical Association*, *81*(396), 991. https://doi.org/10.2307/2289073

Ionescu, D. F., Niciu, M. J., Mathews, D. C., Richards, E. M., & Zarate, C. A. (2013). Neurobiology of anxious depression: A review. *Depression and Anxiety*, *30*(4), 374–385. https://doi.org/10.1002/DA.22095

Jesulola, E., Sharpley, C. F., & Agnew, L. L. (2016). *The effects of gender and depression severity on the association between alpha asymmetry and depression across four brain regions*, 321, 232-239 https://doi.org/10.1016/j.bbr.2016.12.035

Jesulola, E., Sharpley, C. F., Bitsika, V., Agnew, L. L., & Wilson, P. (2015). Frontal alpha asymmetry as a pathway to behavioural withdrawal in depression: Research findings and issues. *Behavioural Brain Research*, *292*, 56–67. https://doi.org/10.1016/J.BBR.2015.05.058

Jog, M. v., Wang, D. J. J., & Narr, K. L. (2019). A review of transcranial direct current stimulation (tDCS) for the individualized treatment of depressive symptoms. *Personalized Medicine in Psychiatry*, *17–18*, 17–22. https://doi.org/10.1016/J.PMIP.2019.03.001

Kaiser, A. K., Doppelmayr, M., & Iglseder, B. (2018). Electroencephalogram alpha asymmetry in geriatric depression. Valid or vanished? *Zeitschrift Fur Gerontologie Und Geriatrie*, *51*(2), 200–205. https://doi.org/10.1007/S00391-016-1108-Z

Kaiser, A. K., Gnjezda, M. T., Knasmüller, S., & Aichhorn, W. (2018). Electroencephalogram alpha asymmetry in patients with depressive disorders: Current perspectives. *Neuropsychiatric Disease and Treatment*, *14*, 1493–1504. https://doi.org/10.2147/NDT.S137776

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in Major Depressive Disorder: Meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, *72*(6), 603. https://doi.org/10.1001/JAMAPSYCHIATRY.2015.0071

Kentgen, L. M., Tenke, C. E., Pine, D. S., Fong, R., Klein, R. G., & Bruder, G. E. (2000). Electroencephalographic asymmetries in adolescents with major depression: Influence of comorbidity with anxiety disorders. *Journal of Abnormal Psychology*, *109*(4), 797–802. https://doi.org/10.1037/0021-843X.109.4.797

Kessler, R. C., Sampson, N. A., Berglund, P., Gruber, M. J., Al-Hamzawi, A., Andrade, L., Bunting, B., Demyttenaere, K., Florescu, S., de Girolamo, G., Gureje, O., He, Y., Hu, C., Huang, Y., Karam, E., Kovess-Masfety, V., Lee, S., Levinson, D., Medina Mora, M. E., … Wilcox, M. A. (2015). Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiology and Psychiatric Sciences*, *24*(3), 210. https://doi.org/10.1017/S2045796015000189

Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research*, *201*(2), 239. https://doi.org/10.1016/J.BBR.2009.03.004

Koller-Schlaud, K., Querbach, J., Behr, J., Ströhle, A., & Rentzsch, J. (2020). Test-Retest Reliability of Frontal and Parietal Alpha Asymmetry during Presentation of Emotional Face Stimuli in Healthy Subjects. *Neuropsychobiology*, *79*(6), 428–436. https://doi.org/10.1159/000505783

Koo, P. C., Berger, C., Kronenberg, G., Bartz, J., Wybitul, P., Reis, O., & Hoeppner, J. (2019). Combined cognitive, psychomotor and electrophysiological biomarkers in major depressive disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *269*(7), 823–832.

https://doi.org/10.1007/S00406-018-0952-9

Laufs, H., Kleinschmidt, A., Beyerle, A., Eger, E., Salek-Haddadi, A., Preibisch, C., & Krakow, K. (2003). EEG-correlated fMRI of human alpha activity. *NeuroImage*, *19*(4), 1463–1476. https://doi.org/10.1016/S1053-8119(03)00286-6

Lewis, R. S., Weekes, N. Y., & Wang, T. H. (2007). The effect of a naturalistic stressor on frontal EEG asymmetry, stress, and health. *Biological Psychology*, *75*(3), 239–247. https://doi.org/10.1016/J.BIOPSYCHO.2007.03.004

Lin, I. M., Chen, T. C., Lin, H. Y., Wang, S. Y., Sung, J. L., & Yen, C. W. (2021). Electroencephalogram patterns in patients comorbid with major depressive disorder and anxiety symptoms: Proposing a hypothesis based on hypercortical arousal and not frontal or parietal alpha asymmetry. *Journal of Affective Disorders*, *282*, 945–952. https://doi.org/10.1016/J.JAD.2021.01.001

Mathersul, D., Williams, L. M., Hopkinson, P. J., & Kemp, A. H. (2008). Investigating models of affect: relationships among EEG alpha asymmetry, depression, and anxiety. *Emotion (Washington, D.C.)*, *8*(4), 560–572. https://doi.org/10.1037/A0012811

Mennella, R., Patron, E., & Palomba, D. (2017). Frontal alpha asymmetry neurofeedback for the reduction of negative affect and anxiety. *Behaviour Research and Therapy*, *92*, 32–40. https://doi.org/10.1016/J.BRAT.2017.02.002

Metzen, D., Genç, E., Getzmann, S., Larra, M. F., Wascher, E., & Ocklenburg, S. (2021). Frontal and parietal EEG alpha asymmetry: a large-scale investigation of short-term reliability on distinct EEG systems. *Brain Structure and Function 2021*, *1*, 1–16. https://doi.org/10.1007/S00429-021-02399-1

Metzger, L. J., Carson, M. A., Paulus, L. A., Paige, S. R., Lasko, N. B., Pitman, R. K., & Orr, S. P. (2004). PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. *Journal of Abnormal Psychology*, *113*(2), 324–329. https://doi.org/10.1037/0021-843X.113.2.324

Mitchell, A. M., & Pössel, P. (2012). Frontal brain activity pattern predicts depression in adolescent boys. *Biological Psychology*, *89*(2), 525–527. https://doi.org/10.1016/J.BIOPSYCHO.2011.12.008

Novick, D., Montgomery, W., Vorstenbosch, E., Moneta, M. V., Dueñas, H., & Haro, J. M. (2017). Recovery in patients with major depressive disorder (MDD): results of a 6-month, multinational, observational study. *Patient Preference and Adherence*, *11*, 1859. https://doi.org/10.2147/PPA.S138750

Nusslock, R., Shackman, A. J., Harmon-Jones, E., Alloy, L. B., Coan, J. A., & Abramson, L. Y. (2011). Cognitive Vulnerability and Frontal Brain Asymmetry: Common Predictors of First Prospective Depressive Episode. *Journal of Abnormal Psychology*, *120*(2), 497. https://doi.org/10.1037/A0022940

Nusslock, R., Shackman, A. J., McMenamin, B. W., Greischar, L. L., Davidson, R. J., & Kovacs, M. (2018). Comorbid anxiety moderates the relationship between depression history and prefrontal EEG asymmetry. *Psychophysiology*, *55*(1). https://doi.org/10.1111/PSYP.12953

Nusslock, R., Walden, K., & Harmon-Jones, E. (2015). Asymmetrical frontal cortical activity associated with differential risk for mood and anxiety disorder symptoms: An RDoC perspective. *International Journal of Psychophysiology*, *98*(2), 249–261. https://doi.org/10.1016/J.IJPSYCHO.2015.06.004

Palmiero, M., & Piccardi, L. (2017). Frontal EEG Asymmetry of Mood: A Mini-Review. *Frontiers in Behavioral Neuroscience*, *11*, 224. https://doi.org/10.3389/FNBEH.2017.00224

Papousek, I., Weiss, E. M., Schulter, G., Fink, A., Reiser, E. M., & Lackner, H. K. (2014). Prefrontal EEG alpha asymmetry changes while observing disaster happening to other people: Cardiac correlates and prediction of emotional impact. *Biological Psychology*, *103*, 184–194.

https://doi.org/10.1016/J.BIOPSYCHO.2014.09.001

Koo P.C., Berger C., Kronenberg G., Bartz J., Wybitul P., Reis O., Hoeppner J. (2019). Combined cognitive, psychomotor and electrophysiological biomarkers in major depressive disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *269*(7), 823–832. https://doi.org/10.1007/S00406-018-0952-9

Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage*, *198*, 181–197. https://doi.org/10.1016/J.NEUROIMAGE.2019.05.026

Pitsillou, E., Bresnehan, S. M., Kagarakis, E. A., Wijoyo, S. J., Liang, J., Hung, A., & Karagiannis, T. C. (2020). The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. *Molecular Biology Reports*, *47*(1), 753–770. https://doi.org/10.1007/S11033-019-05129-3

Quinn, C. R., Rennie, C. J., Harris, A. W. F., & Kemp, A. H. (2014). The impact of melancholia versus non-melancholia on resting-state, EEG alpha asymmetry: electrophysiological evidence for depression heterogeneity. *Psychiatry Research*, *215*(3), 614–617. https://doi.org/10.1016/J.PSYCHRES.2013.12.049

Quintão, S., Delgado, A. R., & Prieto, G. (2013). *Validity Study of the Beck Anxiety Inventory (Portuguese version) by the Rasch Rating Scale Model. Psychological Assessment*, 26(2), 305-310. https://doi.org/10.1590/S0102-79722013000200010

Reznik, S. J., & Allen, J. J. B. (2018). Frontal asymmetry as a mediator and moderator of emotion: An updated review. *Psychophysiology*, *55*(1). https://doi.org/10.1111/PSYP.12965

Rizvi, S., & Khan, A. M. (2019). Use of Transcranial Magnetic Stimulation for Depression. *Cureus*, *11*(5). https://doi.org/10.7759/CUREUS.4736

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *The American Journal of Psychiatry*, *163*(11), 1905–1917. https://doi.org/10.1176/AJP.2006.163.11.1905

Schultz, D. H., Ito, T., Solomyak, L. I., Chen, R. H., Mill, R. D., Anticevic, A., & Cole, M. W. (2019). Global connectivity of the fronto-parietal cognitive control network is related to depression symptoms in the general population. *Network Neuroscience*, *3*(1), 107. https://doi.org/10.1162/NETN_A_00056

Siddiqi, S. H., Taylor, S. F., Cooke, D., Pascual-Leone, A., George, M. S., & Fox, M. D. (2020). Distinct symptom-specific treatment targets for circuit-based neuromodulation. *American Journal of Psychiatry*, *177*(5), 435–446. https://doi.org/10.1176/APPI.AJP.2019.19090915.

Smith, E. E., Cavanagh, J. F., Allen, J. J. B., Correspondence, E., & Smith, M. A. (2017). *Intracranial source activity (eLORETA) related to scalp-level asymmetry scores and depression status*. https://doi.org/10.1111/psyp.13019

Smith, E. E., Zambrano-Vazquez, L., Allen, J. J., & Smith, E. (2016). Patterns of alpha asymmetry in those with elevated worry, trait anxiety, and obsessive-compulsive symptoms*:* A test of the worry and avoidance models. *Neuropsychologia, 85, 118-26.* https:// doi: 10.1016/j.neuropsychologia.2016.03.010.

Spellman, T., & Liston, C. (2020). Toward circuit mechanisms of pathophysiology in depression. *American Journal of Psychiatry*, *177*(5), 381–390. https://doi.org/10.1176/APPI.AJP.2020.20030280

Stewart, J. L., Bismark, A. W., Towers, D. N., Coan, J. A., & Allen, J. J. B. (2010). Resting frontal EEG asymmetry as an endophenotype for depression risk: sex-specific patterns of frontal brain asymmetry. *Journal of Abnormal Psychology*, *119*(3), 502–512.

https://doi.org/10.1037/A0019196

Stewart, J. L., Coan, J. A., Towers, D. N., & Allen, J. J. B. (2014). Resting and task-elicited prefrontal EEG alpha asymmetry in depression: Support for the capability model. *Psychophysiology*, *51*(5), 446–455. https://doi.org/10.1111/PSYP.12191

Stewart, J. L., Towers, D. N., Coan, J. A., & Allen, J. J. B. (2011). The oft-neglected role of parietal EEG asymmetry and risk for major depressive disorder. *Psychophysiology*, *48*(1), 82–95. https://doi.org/10.1111/J.1469-8986.2010.01035.X

Strawbridge, R., Young, A. H., & Cleare, A. J. (2017). Biomarkers for depression: Recent insights, current challenges and future prospects. *Neuropsychiatric Disease and Treatment*, *13*, 1245–1262. https://doi.org/10.2147/NDT.S114542

Sutton, S. K., & Davidson, R. J. (2016). Prefrontal Brain Asymmetry: A Biological Substrate of the Behavioral Approach and Inhibition Systems. *Psychological Science*, *8*(3), 204–210. https://doi.org/10.1111/J.1467-9280.1997.TB00413.X

Szumska, I., Gola, M., Rusanowska, M., Krajewska, M., Żygierewicz, J., Krejtz, I., Nezlek, J. B., & Holas, P. (2021). Mindfulness-based cognitive therapy reduces clinical symptoms, but do not change frontal alpha asymmetry in people with major depression disorder. *International Journal of Neuroscience*, *131*(5), 453–461. https://doi.org/10.1080/00207454.2020.1748621

Tenke, C. E. (2000). Electroencephalographic asymmetries in adolescents with major depression: Influence of comorbidity with anxiety disorders. *Journal of Abnormal Psychology*. https://doi.org/10.1037/0021-843X.109.4.797

The Institute for Health Metrics and Evaluation (2019). Global Burden of Disease. Global Health Data Exchange. Retrieved June 2, 2022, from https://vizhub.healthdata.org/gbd-results/?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b

Thibodeau, R., Jorgensen, R. S., & Kim, S. (2006). Depression, Anxiety, and Resting Frontal EEG Asymmetry: A Meta-Analytic Review. *Journal of Abnormal Psychology*, 115(4), 715-729. https://doi.org/10.1037/0021-843X.115.4.715

Towers, D. N., & Allen, J. J. B. (2009). A better estimate of the internal consistency reliability of frontal EEG asymmetry scores. *Psychophysiology*, *46*(1), 132–142. https://doi.org/10.1111/J.1469-8986.2008.00759.X

Tukey, J. W. (1962). The Future of Data Analysis. *Source: The Annals of Mathematical Statistics*, *33*(1), 1–67.

van der Vinne, N., Vollebregt, M. A., van Putten, M. J. A. M., & Arns, M. (2017). Frontal alpha asymmetry as a diagnostic marker in depression: Fact or fiction? A meta-analysis. *NeuroImage: Clinical*, *16*, 79–87. https://doi.org/10.1016/J.NICL.2017.07.006

Volf, N. v., & Passynkova, N. R. (2002). EEG mapping in seasonal affective disorder. *Journal of Affective Disorders*, *72*(1), 61–69. https://doi.org/10.1016/S0165-0327(01)00425-6

Wei, X., Shen, H., Ren, J., Li, X., Xu, X., Yang, R., Lai, L., Chen, L., Hu, J., Liu, W., & Jiang, X. (2014). Altered Resting-State Connectivity in College Students with Nonclinical Depressive Symptoms. *PLoS ONE*, *9*(12), e114603. https://doi.org/10.1371/JOURNAL.PONE.0114603

Wheeler, R. E., Davidson, R. J., & Tomarken, A. J.(1993). Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology*, *30*(1), 82–89. https://doi.org/10.1111/J.1469-8986.1993.TB03207.X

Universidade do Minho

SECVS

Subcomissão de Ética para as Ciências da Vida e da Saúde

Identificação do documento: SECVS 174/2017

Título do projeto: *Transcranial Direct Current Stimulation as add-on treatment to Cognitive-Behavior Therapy in first episode Major Depression drug-naive patients (ESAP Trial)*

Investigador(a) responsável: Sandra Carvalho, da Escola de Psicologia da Universidade do Minho

Outros investigadores: Jorge Leite, da Escola de Psicologia da Universidade do Minho e do Instituto de Desenvolvimento Humano Portucalense (INPP) da Universidade Portucalense; Óscar F. Gonçalves da Escola de Psicologia da Universidade do Minho

Subunidade orgânica: Centro de Investigação em Psicologia (CIPsi), Universidade do Minho, Braga, Portugal

PARECER

A Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS) analisou o processo relativo ao projeto intitulado *Transcranial Direct Current Stimulation as add-on treatment to Cognitive-Behavior Therapy in first episode Major Depression drug-naive patients (ESAP Trial).*

Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na experimentação com humanos, em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde.

Face ao exposto, a SECVS nada tem a opor à realização do projeto.

Braga, 30 de janeiro de 2018.

A Presidente

Maria Cecília de Lemos Pinto Estrela Leão