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ALTERAÇÕES ELETROFISIOLÓGICAS EM PACIENTES COM TRANSTORNO DE PÂNICO MEDIDAS POR MEIO DE UM VÍDEO DE REALIDADE VIRTUAL E PELA TAREFA *ODDBALL*

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Orientadora: Profa. Dra. Bruna Brandão Velasques

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Dissertação de Mestrado submetida ao corpo docente do Programa de Pós-Graduação em Saúde Mental do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro – UFRJ, como parte dos requisitos necessários à obtenção do grau de Mestre em Saúde Mental.

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RESUMO

OBJETIVO. Esta dissertação tem como objetivo apresentar três artigos que investigaram as alterações eletrocorticais em pacientes com transtorno de pânico (TP), tendo em vista uma melhor compreensão sobre possíveis prejuízos no processamento de informações nos pacientes com este transtorno. O primeiro consistiu em uma revisão sistemática sobre o comportamento do componente P300 e TP, a qual será apresentada para uma melhor contextualização do tema, enquanto os outros dois artigos foram elaborados a partir de uma investigação experimental conduzida através da Eletroencefalografia Quantitativa (EEGq). Neste sentido, foi investigada a influência da ansiedade durante a execução de uma tarefa sensoriomotora que avalia funções executivas e o controle inibitório em pacientes com TP. **MÉTODO.** Os sinais eletrofisiológicos foram captados para observar as diferenças entre pacientes com TP e sujeitos saudáveis na coerência em gama e na potência absoluta de alfa durante a execução de uma tarefa sensoriomotora baseada no paradigma *oddball*. Esta tarefa foi realizada antes e após a apresentação de um filme de realidade virtual com cenas relacionadas ao TP. Uma ANOVA *two-way* foi empregada para avaliar a coerência de gama para os fatores grupo e momento. A mesma metodologia foi aplicada na análise estatística da potência absoluta de alfa. **RESULTADOS.** Para coerência em gama, foi encontrada uma diferença estatística para grupo nos seguintes pares de eletrodos: F4-F8, Fp2-F4, F4-P4, F7-F3 e P3-Pz; enquanto para o fator momento foi encontrada diferença significativa somente nos pares de eletrodos F3-P3. Para a potência absoluta em alfa, foi encontrada interação entre os fatores grupo e momento nos eletrodos: Fp1, F3, F7, Fz, P4, Pz, T3, T4 e T6; efeito principal para os fatores grupo e momento nos eletrodos Fp2, F4, F8 e P3; e efeito principal para o fator momento no eletrodo T5. **DISCUSSÃO.** Os dados encontrados no presente estudo confirmam a hipótese de que pacientes com TP apresentam prejuízo no processamento de informações, o que foi ilustrado pela maior coerência em gama que pode estar associada a uma interferência na comunicação entre áreas cerebrais, pela menor potência absoluta de alfa apresentadas pelos pacientes com TP. Tais resultados se associam com os resultados da revisão sistemática, que aponta para um prejuízo nas habilidades de atenção, processamento de informações e inabilidade em respostas automáticas e na interpretação de estímulos internos e externos relacionados com o transtorno.

Palavras-chave: Transtorno de Pânico; Paradigma *oddball;* EEGq; P300*;* Coerência em gama; Potência absoluta de alfa; Realidade virtual.

ABSTRACT

OBJECTIVE. The present study aimed to present three articles that investigated eletrocortical alterations in patients with panic disorder (PD) to better understand the impairments in the information processing. The first paper was a systematic review about the P300 component and PD, what will be presented to the contextualization of the theme. The others two articles were written after an experimental investigation that used the quantitative electroencephalography (qEEG). In this way, we investigated the influence of anxiety during the execution of a sensorimotor task that evaluates executive functions and the inhibitory control in PD patients. **METHOD.** The electrophysiological signs were recorded to observe differences between PD patients and healthy controls (HC) in the gamma coherence and absolute alpha power during the execution of a sensorimotor task based on the *oddball* paradigm. This task were performed before and after the presentation of a virtual reality movie related to PD. An ANOVA *two-way* were applied to examine the gamma coherence for the factors group and moment. The same methodology was used in the statistical analysis of absolute alpha power. **RESULTS.** In the gamma coherence analysis, we found a significant difference for group in the electrode pairs: F4-F8, Fp2-F4, F4-P4, F7-F3 and P3-Pz; and for moment in F3-P3 electrodes. In the statistical analysis of absolute alpha power, we found an interaction between the factors in the electrodes: Fp1, F3, F7, Fz, P4, Pz, T3, T4 and T6. We also observe a significant difference for group and moment in the electrodes Fp2, F4, F8 and P3. While in the electrode T5 we found a main effect for moment. **DISCUSSION.** Our results confirm the previous hypothesis, that PD patients present impairment in the information processing. Which were demonstrated by the higher gamma coherence, that could be related to and interference on the communication between the brain areas, and by the lower absolute alpha power presented by the PD patients. Those results can be associated with the systematic review, that pointed the prejudice in the attention, in the information processing and an inability to automatically respond and interpret internal and external stimuli related to the disorder.

Key words: Panic disorder; *Oddball* Paradigm; EEGq; P300; Gamma Coherence; Absolute Alpha Power; Information Processing; Virtual Reality.

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Capítulo I – O Problema

1.1. Introdução

O Transtorno de Pânico (TP) e suas bases cognitivas, comportamentais e neurobiológicas vêm sendo amplamente investigados nos últimos anos. O TP é um transtorno de ansiedade de grande prevalência na sociedade (Kessler *et al*., 2005), cujos sintomas podem impactar na saúde e na qualidade de vida daqueles que o possuem (Hollifield *et al*., 1997), causando dificuldade ou até mesmo incapacitação profissional e nas relações sociais. Os pacientes diagnosticados com TP sofrem de repetidos e inesperados ataques de intensa ansiedade, os quais não se restringem a determinadas situações ou circunstâncias, podendo resultar nos seguintes sintomas: medo de morrer e perder o controle, sensação de falta de ar, palpitações, taquicardia, entre outros.

Pesquisadores (Maddock *et al*., 2003; Pfleiderer *et al*., 2007; Chechko *et al*., 2009; Lopes *et al*., 2010; De Carvalho *et al*., 2013) têm investigado o funcionamento neurobiológico do TP através de estudos neurofisiológicos e de neuroimagem. O modelo descrito por Gorman *et al*. (2000) associa o condicionamento do medo em pacientes com TP com déficits nos mecanismos *top-down* de controle inibitório. Déficits no processamento de estímulos possibilitam uma ativação aumentada na amígdala que, por sua vez, transmite *outputs* para estruturas que podem selecionar e ativar respostas autonômicas, comportamentais e endócrinas de medo, dando origem a sintomas de ansiedade que podem configurar um ataque de pânico (de Carvalho *et al*., 2013). Este modelo neurobiológico do TP é muito coerente com o modelo cognitivo deste transtorno, já que este descreve que o processamento inadequado dos estímulos externos e sensoriais pode gerar um medo condicionado capaz de ativar o sistema simpático, o que é interpretado como uma confirmação do perigo (Rangé & Borba, 2008).

Com o objetivo de investigar aspectos cognitivos e neurobiológicos de transtornos de ansiedade, pesquisadores (Enoch *et al*., 1995; Clark *et al*., 2009; De Carvalho *et al*., 2013) têm utilizado a eletroencefalografia quantitativa (EEGq) para observar, através dos sinais eletrofisiológicos, alterações corticais em pacientes ansiosos. Windmann *et al*. (2002) destacou em seu estudo que na ansiedade ocorre uma interação disfuncional entre o córtex pré-frontal e o sistema límbico. Portanto, para melhor investigar tal interação, optamos por utilizar duas medidas de EEG no domínio da frequência: coerência em gama e potência absoluta de alfa.

A banda gama (30 a 80 Hz) é frequentemente associada com processos cognitivos (Herrmann *et al*., 2010) e tem sido utilizada como medida de integração da informação sensorial durante o estágio pré-atentivo do processamento de informação (Karakas & Basar, 1998; Behrendt & Young, 2004). A sincronização da oscilação em gama está relacionada com a comunicação córtico-cortical de conjuntos de neurônios que participam do funcionamento cognitivo integrado, o que é conhecido como fenômeno *binding*. Este mecanismo contribui para a formação de processos cognitivos conscientes, como a memória, atenção e percepção (Herrmann *et al*, 2010; Velasques, 2013).

Já a banda alfa (8-13Hz) é uma frequência predominante em estados de relaxamento ou de "ausência de atividade" em uma determinada região cerebral. A potência absoluta da oscilação de alfa diminui quando há esforço cognitivo ou direcionamento da atenção (Niedermeyer, 2005). Portanto, esta medida vem sendo utilizada na investigação sobre prejuízos no processamento cognitivo em pacientes com transtornos de ansiedade, uma vez que pesquisadores acreditam que a diminuição da potência absoluta de alfa se relaciona com o estado de aumento da excitação cortical (Wiedemann *et al*., 1998; Gordeev, 2008; Wise *et al*., 2011) e, consequentemente, no prejuízo de funções *top-down* e de controle inibitório (Gordeev, 2008; Pavlenko *et al*., 2009).

Neste contexto, o presente estudo justifica-se pela importância da investigação de medidas eletroencefalográficas associadas a possíveis alterações eletrocorticais em pacientes com TP, as quais serão avaliadas durante uma tarefa de acordo com o paradigma *oddball* a ser realizada antes e depois da exposição a um vídeo de realidade virtual com estímulos ansiogênicos. A hipótese inicial era que os pacientes com TP apresentariam aumento na ansiedade após a apresentação do vídeo de realidade virtual, o que lhes traria prejuízo na ativação e comunicação das redes frontais, parietais e temporais, o que afetaria a memória de trabalho. Sendo assim, o objetivo da dissertação é apresentar um artigo de revisão que servirá como plano de fundo na contextualização do problema, e mais dois artigos experimentais que, através de duas diferentes medidas (potência absoluta de alfa e coerência em gama), investigaram a influência da ansiedade durante a execução de uma tarefa sensoriomotora que avalia funções executivas e o controle inibitório em pacientes com TP.

CAPÍTULO II – Fundamentação Teórica:

2.1. Transtorno de Pânico:

O Transtorno de Pânico (TP) é um distúrbio psiquiátrico considerado crônico, recorrente, de relevante prevalência na sociedade (Kessler *et al*., 2005) e que provoca grande impacto na qualidade de vida (Hollifield *et al*., 1997), aumentando o risco de suicídio (Lim *et al*., 2015). Neste transtorno, de acordo com o DSM-V (2013), ocorrem repetidos ataques inesperados de intensa ansiedade – ataques de pânico (AP) - que não se restringem a uma situação ou circunstância determinada, nos quais devem estar presentes pelo menos quatro sintomas cognitivos ou somáticos, como: o medo de morrer, o medo de perder o controle e enlouquecer, despersonalização, desrealização, dor e/ou desconforto torácico, palpitações e taquicardia, sensação de falta de ar, asfixia, tremores, sudorese, tontura, ondas de calor, náusea, parestesias, entre outros. Um AP pode ser desencadeado por um estímulo visoespacial e/ou auditivo, assim como por cognições catastróficas (Coplan e Lydiard, 1998). Em geral, estas crises duram alguns minutos, mas podem ser mais prolongadas. Para o diagnóstico de TP, os AP devem ser acompanhados, por pelo menos um mês, de no mínimo uma das seguintes características: ansiedade ou medo de novos ataques de pânico, mudança comportamental significativa devido aos ataques ou preocupação sobre as consequências de novos ataques.

A base neurobiológica do TP tem sido estudada através da descrição do funcionamento de um neurocircuito do medo (Gorman *et al*., 2000), o qual aponta que pacientes com TP sofrem prejuízo nos mecanismos *top-down* de controle inibitório. A rede cerebral que envolve o processamento da aquisição do medo condicionado, a qual estaria supostamente envolvida no TP, é ativada no tálamo anterior, estrutura na qual chegam informações sensoriais do estímulo condicionado (LeDoux *et al*., 1990). De acordo com este modelo estudado por Gorman *et al*. (2000), déficits no processamento de estímulos no tronco cerebral e em outras regiões corticais responsáveis pelo processamento de informação, podem levar à ativação aumentada da amígdala. Esta estrutura é um centro onde convergem muitos *inputs* sensoriais, entretanto, também transmite, a partir de seu núcleo central, *outputs* para o hipotálamo, áreas do mesencéfalo e tronco cerebral que podem selecionar e ativar respostas autonômicas, comportamentais e endócrinas de medo, envolvidas no AP (Misslin, 2003; Garakani *et*

al., 2006). A ativação da amígdala pode ser consequência de uma má interpretação das informações sensoriais, o que possibilita que uma cascata de respostas neuronais seja experimentada, tal como o AP (de Carvalho *et al*., 2013). Estudos de neuroimagem e mapeamento cerebral têm apontado evidências para esta hipótese (Dantendorfer *et al*., 1996; Maddock *et al*., 2003; Pillay *et al*., 2006; Pfleiderer *et al*., 2007; Chechko *et al*., 2009; Lopes *et al*., 2010).

A base cognitiva do TP baseia-se na interpretação disfuncional das sensações corporais (Clark, 1986) e um processamento inadequado (de "catastrofização") das informações de um estímulo externo (Pauli *et al*., 1997). Assim, segundo o modelo cognitivo do TP, a interpretação de um estímulo que é entendido como perigoso gera uma apreensão, que dispara a ativação simpática e consequentes sensações corporais. Estas são então interpretadas como uma "confirmação do perigo", produzindo uma ansiedade ainda maior (Rangé & Borba, 2008).

As hipóteses neurobiológicas do TP são coerentes com as hipóteses de processamento cognitivo, pois muitos estudiosos associam a ansiedade a uma interação disfuncional entre o córtex pré-frontal e o sistema límbico (Windmann *et al*., 2002). O córtex pré-frontal está relacionado com a função executiva, flexibilidade cognitiva, memória de trabalho (De Carvalho *et al*., 2010), planejamento de comportamentos e pensamentos complexos, como tomadas de decisão, controle atencional (Bechara *et al*., 1997; Damasio, 1994), modulação do comportamento (Waltz *et al*., 1999; Windmann, 2002), regulação emocional (Windmann, 2002; Lobo *et al*., 2011). A regulação de processos atencionais, interpretativos e associativos relacionados a pistas de ameaça parece estar comprometida na ansiedade.

As diferenças de ativação neuroanatômicas observadas em pacientes com TP levaram ao questionamento: quais são os déficits cognitivos relacionados a este transtorno? Uma revisão sistemática conduzida por O'Sullivan & Newman (2014) indicou uma ausência de dificuldades neuropsicológicas quando compactou pacientes com pânico e controles saudáveis. Contudo, outros autores apontaram que apareceu algum suporte para o prejuízo nas funções de memória verbal e visual de curto prazo, comparando as amostras. Dratcu e Bond (1998) ressaltaram que déficits na memória de trabalho e memória explícita podem estar relacionados ao estado de grande excitação e ansiedade durante a execução da tarefa solicitada em sua pesquisa. Danos na memória de trabalho poderiam estar relacionados à dificuldade no processamento de informação

apresentada por pacientes com TP e, consequentemente, à disfunção na interpretação dos sintomas corporais.

Neste contexto, resultados de diferentes pesquisas sobre a performance da memória de trabalho em pacientes com pânico são controversos, pois alguns demonstram que pacientes com esta desordem não apresentam dificuldades na memória de trabalho (Boldrini *et al*., 2005; Deckersbach *et al*., 2011), enquanto outros afirmam que há prejuízo nesta função cognitiva (Dratcu and Bond, 1998). Por isso, novas pesquisas ainda precisam investigar melhor esta função cognitiva em pacientes com TP, utilizando amostras maiores, para uma melhor compreensão de como se manifesta neste contexto.

2.2. Paradigma *Oddball*:

Na década de 70, o paradigma *oddball* surgiu como método para aprofundar os conhecimentos sobre o componente P300 (Squires *et al*., 1975), um potencial evocado relacionado a eventos que consiste em uma medida eletrofisiológica gerada em resposta a um estímulo sensorial. Enquanto pesquisadores estudavam o quanto os padrões elétricos variam em diferentes condições, o paradigma *oddball* surgiu para elucidar os efeitos da percepção da probabilidade de surgimento do estímulo, assim como a sua relevância (Donchin, Ritter, & McCallum, 1978; Polich, 2010). Este paradigma consiste na identificação de estímulos alvo infrequentes, em meio à apresentação de estímulos não-alvo frequentes. Os estímulos mais utilizados nas pesquisas podem ser visuais ou sonoros, onde a possibilidade de aparecimento de um estímulo alvo é de 20%, enquanto a de um estímulo não-alvo é de 80%. Todos os estímulos surgem rapidamente e, diante da percepção do surgimento do estímulo alvo, os participantes devem gerar uma resposta, seja ela motora (ex.: apertar um botão) ou cognitiva (ex.: contar mentalmente). Ao mesmo tempo, devem inibir a resposta ao perceberem o estímulo não-alvo. Desta forma, este paradigma vem sendo utilizado em pesquisas de EEGq, uma vez que possibilita a análise das respostas eletrofisiológicas para o estímulo alvo, comparando-as com as observadas diante dos estímulos não-alvo, o que é entendido como uma medida das diferenças entre os processos cerebrais subjacentes (Huettel & McCarthy, 2004; Damborská *et al*., 2012).

O paradigma *oddball* é um dos experimentos cognitivos mais utilizados em estudos eletrofisiológicos, por meio do qual é realizada a investigação sobre os efeitos da percepção e diferenciação (se relevantes ou não) de novos estímulos no processamento da informação (Herrmann & Knight, 2001; Wise *et al*., 2009). De acordo com Başar *et al*. (2015), o cérebro se envolve em diversas respostas durante a análise do paradigma *oddball*, incluindo respostas sensoriais. Esta tarefa requer um processamento cognitivo do estímulo que desencadeia funções de atenção, percepção, aprendizagem e recordação de traços de memória (Başar *et al*., 2015).

A estimulação do paradigma *oddball* visual consiste numa tarefa cognitiva de atenção e de um sinal sensorial (ex.: estímulo na tela). Segundo Başar *et al*. (2015), é evidente que o estímulo deve ativar diretamente o córtex occipital sobre o tálamo e, paralelamente, o sistema límbico e a rede cognitiva (isto é, áreas de associação, lobos frontais e sistema límbico). O estímulo alvo irá dar origem à ativação de um maior número de estruturas corticais, apesar de mais lentamente do que a ativação que ocorre na região occipital. O estímulo alvo do paradigma *oddball* é complexo, uma vez que elicia uma resposta sensorial e um processamento cognitivo, incluindo a ação da memória de trabalho. Além disso, esse estímulo alvo induz à ordem de emitir uma resposta (Başar *et al*., 2015).

Este paradigma é capaz de evocar respostas que são consideradas como marcadores confiáveis de funções cognitivas, ativando regiões pré-frontais de forma transitória (Polich, 1999). Estudos anteriores indicaram a contribuição das áreas tempo-parietal e frontal em resposta à tarefa *oddball*, observados através dos métodos de EEG (Menon *et al*., 1997) e ressonância magnética funcional (IRMf) (McCarthy *et al*., 1997). Diversas pesquisas com IRMf constataram que a percepção do estímulo alvo provoca a ativação sistemática no córtex pré-frontal e no córtex parietal (Clark *et al*., 2000; Stevens *et al*., 2000; Casey *et al*., 2001; Clark *et al*., 2001), além de provocar um aumento significativo do nível dependente de oxigênio no sangue (BOLD) no giro supramarginal, córtex frontal opercular e insular bilateralmente e, regiões parietal e frontal na condição alvo comparada a não-alvo (Linden *et al*., 1999).

Este paradigma já foi utilizado em pesquisas sobre o transtorno de pânico. Gordeev (2008) analisou funções cognitivas de pacientes com TP, observando o componente P300 na presença de estímulos alvo auditivos, em conformidade com o paradigma *oddball*. Por meio desta metodologia, este pesquisador verificou que estes pacientes apresentaram menor amplitude do componente P300 e prejuízo na sua

habituação em ambos os hemisférios. Uma vez que a amplitude do P300 é diretamente proporcional ao nível de atenção empregada na execução da tarefa e depende da função de memória de trabalho, Gordeev (2008) concluiu que seus resultados podem evidenciar que pacientes com TP sofrem prejuízo na atenção concentrada e memória de curto-prazo.

Já na investigação conduzida por Wise *et al*. (2009), onde também foi utilizado o paradigma *oddball* com estímulos alvo auditivos, foi possível observar que, diante dos estímulos alvo, os pacientes apresentaram menor amplitude do componente P300, reduzida latência, aumento da frequência cardíaca e menor condutância cutânea. Os resultados sugeriram que pacientes com TP apresentam uma inabilidade de alocar apropriadamente recursos neurais aos estímulos, o que pode afetar o processamento de informações, uma vez que pacientes apresentaram dificuldade na discriminação entre estímulos sonoros em um contexto de uma simples tarefa de discriminação auditiva. O que, de acordo com o autor, reflete uma possível redução em diversos níveis de funcionamento, tal como no autonômico, perceptual, comportamental, afetivo, cognitivo e cortical (Wise *et al*.,2009).

Portanto, o paradigma *oddball* vem sendo frequentemente utilizado nas pesquisas de neurociência sobre disfunções no processamento sensorial e cognitivo (İşoğlu-Alkaç *et al*., 2007; Warbrick *et al*., 2013), devido à sua fidedignidade com marcadores de funções cognitivas e fácil aplicabilidade e reprodução.

2.3. Coerência em Gama:

Oscilações neurais vêm sendo medidas e interpretadas de múltiplas formas, a fim de entender melhor possíveis relações funcionais entre a fisiologia, o processamento de informações e a cognição (Buzsáki & Schomburg, 2015). Na eletroencefalografia quantitativa, a função de coerência possibilita a observação do acoplamento funcional entre diferentes áreas corticais (Serrien *et al*., 2004; Szurhaj *et al*., 2005), por meio da quantificação do grau de dependência linear entre dois sinais no domínio da frequência (limitada numa faixa entre 0 e 1) (Gomes *et al*., 2007). A coerência é uma medida que representa a ativação simultânea de duas áreas corticais e, assim sendo, é uma medida de co-ativação de duas ou mais áreas cerebrais. A informação obtida da função de coerência parece ser essencial para o entendimento de como a inter-relação funcional

entre regiões pode mudar diante de diferentes condições ou comportamentos (Anghinah, 2005). Desta forma, é de grande relevância a medição desta função durante a execução de determinadas tarefas que exijam integração sensoriomotora (Minc *et al*., 2010) ou tarefas cognitivas (Fries, 2015).

A oscilação em gama é uma frequência rápida que varia entre 30 e 100 Hz (Hermann *et al*., 2004; Farzan *et al*., 2010; Ozerdem *et al*., 2010; Ozerdem *et al*., 2011, Teixeira *et al*., 2011; Buzsáki & Schomburg, 2015; Li *et al*., 2015). Apesar dos mecanismos neurais geradores da atividade desta banda de frequência não serem totalmente esclarecidos, diferentes relatos têm relacionado sua geração e modulação à neurotransmissão inibitória GABAérgica (Bartos *et al*, 2007; Leung & Shen, 2007). A ação do ácido gama-aminobutírico (GABA) atenua a atividade de outros neurônios, como, por exemplo, dos neurônios piramidais no córtex e desempenha um importante papel na geração da oscilação gama (Farzan *et al*., 2010). Acredita-se que o potencial pós-sináptico inibitório mediado pelo receptor GABAa contribui para a oscilação gama (Bartos *et al*., 2007), enquanto o potencial pós-sináptico inibitório mediado pelo receptor GABAb tem sido associado com a modulação da oscilação gama (Leung & Shen, 2007).

Esta banda de frequência tem despertado o interesse de pesquisadores, devido à sua já documentada relação com processos cognitivos (Herrmann *et al*., 2010), tais como memória de trabalho, integração sensoriomotora e planejamento motor (Müller, 2000; Kim & Kim, 2006; Omlor *et al*., 2007; Minc *et al*., 2010). Contudo, as principais funções cognitivas atribuídas a gama são conexões entre as percepções - *perceptual binding* (Gray *et al*., 1990; Widmann *et al*., 2007) e atenção (Tiitinen *et al*., 1993; Minc *et al*., 2010). Este fenômeno denominado *perceptual binding* é definido pelos mecanismos que possibilitam que diferentes áreas do córtex articulem de forma adequada as diferentes características de objetos complexos, possibilitando a experiência de percepção conscientemente de um objeto único (Reynolds & Desimone, 1999).

O modelo denominado *match-and-utilization* (MUM), assume que, o reconhecimento de um estímulo lembrado (que evoca uma representação anteriormente formada) provoca um aumento da resposta de gama (em torno de 200ms após a apresentação do estímulo), a qual é mais forte do que a induzida pela percepção de novos estímulos (Herrmann *et al*., 2004; Busch *et al*., 2006). Desta forma, mecanismos de memória influenciam na modulação da resposta da oscilação em gama (Herrmann *et*

al., 2004). Além disso, a expectativa do surgimento de certo estímulo também leva ao aumento da atividade evocada em áreas sensoriais primárias (Herrmann *et al*., 2004). É importante ressaltar que acredita-se que outras funções cognitivas associadas à gama são dependentes de processos de memória (Velasques, 2013).

A medida de gama varia de acordo com a resposta gerada e das regiões corticais envolvidas durante tais tarefas (Kilner, 2005; Grossmann, 2008; Whitham, 2008). Ademais, a coerência em gama é capaz de ligar áreas corticais responsáveis por uma determinada função e pode indicar o acoplamento de áreas sensoriomotoras intra e/ou inter hemisféricas (Alegre, 2000). Estudos anteriores reportaram uma redução na coerência em gama como um marcador eletrofisiológico de prejuízo cognitivo (Farzan *et al*., 2010; Velasques *et al*., 2013). Ao mesmo tempo, diversos laboratórios relataram um aumento na oscilação gama durante processos cognitivos (Basar-Eroglu *et al*., 1996; Szurhaj *et al*., 2005; Herrmann *et al*., 2010; Teixeira *et al*., 2011).

Nos últimos anos, a coerência em gama vem sendo amplamente investigada em estudos na área da saúde mental, na investigação sobre transtorno bipolar (Özerdem *et al*., 2011; Velasques *et al*., 2013), esquizofrenia (Li *et al*., 2015) e autismo (Peiker *et al*., 2015). O experimento conduzido por Teixeira *et al*. (2010) utilizou a coerência em gama para elucidar mecanismos corticais envolvidos em ações antecipatórias em uma tarefa de apreensão de bolas em queda livre. Os resultados desta investigação sugeriram que as funções de atenção, planejamento, integração somato-sensorial e informação visual (funções geradas principalmente por áreas frontais) são funções obrigatórias para a preparação motora, percepção e execução do movimento (funções geradas principalmente por áreas centrais). Sendo assim, a coerência em gama é relevante para o entendimento da comunicação entre diferentes áreas cerebrais e, assim, entender melhor como diferente redes podem atuar em conjunto para determinados fins (motor, sensorial ou cognitivo).

A coerência em gama é considerada importante para plasticidade e comunicação neuronal e o seu estudo pode viabilizar um melhor entendimento sobre processos internos de redes neurais envolvidas com funções cognitivas complexas, tais como atenção, memória de trabalho, memória de longo prazo e o fenômeno *binding*. Logo, importantes aspectos da cognição humana podem ser elucidados a partir da investigação da coerência em gama, uma vez que esta atua em diversas regiões do cérebro durante diferentes níveis do processamento.

2.4. Potência Absoluta de Alfa:

A análise da banda alfa tem-se mostrado uma importante ferramenta de investigação do funcionamento cerebral em protocolos que utilizam a execução real de tarefas motoras, tarefas cognitivas ou em imagética motora (Stecklow *et al*., 2007). A banda alfa (8–13 Hz) é uma faixa de frequência do ritmo cerebral predominante em estados de vigília, relaxamento físico e "ausência de atividade" em uma determinada região cerebral, a qual é atenuada pelo esforço cognitivo, permanência de olhos abertos ou atenção (Niedermeyer, 2005).

A potência absoluta é uma medida de EEG que é mensurada de acordo com a amplitude absoluta (microvolts/Hz) específica observada sobre os eletrodos. A magnitude da potência da banda alfa é inversamente relacionada ao grau de esforço cognitivo por uma determinada região cortical, podendo ocorrer aumento de tal medida em áreas não ativas, o que indica seletividade na utilização das redes neuronais durante o processamento de informação (Stecklow *et al*., 2007). Assim, o aumento da potência de alfa representa uma condição de relaxamento ou um estado de baixa excitabilidade (Cahn & Polich, 2006; Gordeev, 2008; Pavlenko *et al*., 2009). A potência absoluta de alfa também pode ser considerada um índice de medição da estabilidade emocional, uma vez que estudos anteriores demonstraram o aparecimento de alfa durante um exercício de meditação, o qual indicou um estado de baixa excitabilidade com a redução do estresse e da ansiedade (Cho *et al*., 2011).

Apesar da escassa evidência da origem neurofisiológica do ritmo alfa, de forma geral, entende-se que a oscilação de alfa pode resultar de um feedback rítmico GABAérgico interneuronal (Lorincz *et al*., 2009). Tal feedback pode provocar a inibição funcional mediada por alfa, silenciando de forma direta o processamento de neurônios piramidais ou reduzindo a eficácia da entrada excitatória (Mann & Paulsen, 2007).

Oscilações neurais e, especificamente, a oscilação de alfa, mudam substancialmente durante o desenvolvimento humano, da infância até o final da adolescência (Uhlhaas *et al*., 2009). Tais mudanças na atividade de alfa tendem a se estabilizar no início da vida adulta, assim, a estabilidade no padrão de alfa é uma característica do cérebro adulto (Eidelman-Rothman *et al*., 2016).

Este ritmo de oscilação possui uma relação com o processo *top-down* e controle inibitório (Klimesch *et al*., 2007), e é eliciado em situações em que sujeitos controlam

ou inibem a execução de uma resposta (De Carvalho *et al*., 2013). Klimesch *et al*. (2007) sugeriram que o aumento da potência de alfa relacionado à tarefa reflete o processo *top-down*, o controle inibitório de dados irrelevantes para a realização da tarefa. Enquanto outros autores apontaram que o aumento de alfa pode refletir o processamento ativo (relacionado à memória) (Palva & Palva, 2007).

O traço de déficit na atividade de alfa vem sendo proposto como um fator de risco para diversos transtornos psiquiátricos, incluindo transtornos de ansiedade e alcoolismo (Propping *et al*., 1980). A potência absoluta de alfa vem sendo pesquisada na investigação sobre processamento cognitivo em diferentes transtornos de ansiedade (De Carvalho *et al*., 2013). Pesquisas anteriores verificaram que uma diminuição na potência absoluta de alfa é relacionada com o estado de aumento na excitação cortical (Wiedemann *et al*., 1998; Gordeev, 2008; Wise *et al*., 2011). Estudos sobre potência absoluta de alfa e transtorno de pânico reportaram que pacientes com este diagnóstico apresentaram menor potência de alfa, quando comparados com controles saudáveis (Siciliani *et al*., 1975; Enoch *et al*., 1995; Kalashnikova & Sorokina, 1995; Wiedemann *et al*., 1998; Gordeev, 2008; Wise *et al*., 2011, De Carvalho *et al*., 2013).

No experimento conduzido por De Carvalho *et al*. (2013), sujeitos saudáveis apresentaram maior potência absoluta de alfa na área frontal, quando comparados com pacientes com TP, o que foi interpretado como um possível prejuízo dos pacientes na regulação frontal da excitação originada de regiões subcorticais mais profundas. Acredita-se que essa diminuição da potência absoluta de alfa pode estar relacionado à uma disfunção no circuito talâmico-cortical, o qual é associado com uma dificuldade na inibição de informações irrelevantes, que é um papel desempenhado especialmente pelo córtex pré-frontal (Klimesch *et al*., 2007). Este entendimento pode estar relacionado com a hipótese de que estes pacientes apresentam um processamento disfuncional de estímulos externos (Pauli *et al*., 1997) e sensações corporais (Clark, 1986).

Além disso, uma diminuição na potência absoluta de alfa pode afetar funções *top-down*, portanto os pacientes com TP podem apresentar prejuízo na regulação *top-down* e no controle inibitório durante o estado de ansiedade, o que estaria relacionado com o já observado estado de alta excitabilidade e diminuição no controle inibitório (Gordeev, 2008; Pavlenko *et al*., 2009).

Se o controle *top-down* do córtex pré-frontal não está trabalhando apropriadamente, sintomas de ansiedade tendem a ser mais proeminentes (De Carvalho *et al*., 2013). Enquanto a diminuição da potência absoluta de alfa representa um estado

de alta excitabilidade, o aumento desta potência comumente observada em controles saudáveis podem estar relacionada com um estado de menor excitabilidade (Gordeev, 2008). Logo, o estudo sobre a potência absoluta de alfa pode contribuir para um melhor entendimento do processamento de informação e transtornos de ansiedade.

Capítulo III – Metodologia:

A revisão sistemática foi realizada durante o período de estágio probatório, enquanto o procedimento e a tarefa experimental utilizados na presente dissertação foram desenvolvidos durante o mestrado da autora. A seguir será descrita a metodologia da pesquisa experimental randomizada pareada que deu origem aos artigos II e III de forma detalhada.

3.1. Amostra

A amostra foi composta por dez controles saudáveis (1 homem e 9 mulheres com média etária de 38.2 anos, DP: 13.69), todos destros, e nove pacientes com pânico (9 mulheres com média etária de 48.8 anos, DP: 11.16), sendo oito destros e um sinistro. Todos os participantes tinham idades variando entre 20 e 60 anos de idade. Os pacientes foram convidados a participar do estudo no Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB) e na Divisão de Psicologia Aplicada (UFRJ), após uma entrevista estruturada com os instrumentos MINI (Mini International Neuropsychiatric Interview 5.0) e SCID II (versão brasileira: 1.0) que confirmava o diagnóstico de TPA de acordo com o DSM-V (Diagnostic and Statistical Manual of Psychiatric Disorders – 5ª edição, 2013), contudo foram excluídos deste estudo pacientes com outras comorbidades. Era solicitado aos pacientes que suspendessem a medicação um dia antes do exame, para evitar possível viés farmacológico nos sinais eletrofisiológicos. Os participantes do grupo controle incluídos no estudo eram sadios, sem nenhuma condição psiquiátrica presente ou anterior e, além disso, não deveriam fazer uso de qualquer substância psicotrópica ou psicoativa. Estes eram avaliados através de uma entrevista e de um questionário detalhado, a fim de identificar e excluir do experimento qualquer sujeito que pudesse contaminar futuros resultados. Os sujeitos do grupo controle foram convidados a participar do estudo no Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB). Todos os participantes tinham visão normal ou visão corrigida e nenhuma deficiência física e/ou mental. Os participantes preencheram o consentimento livre e esclarecido, onde as condições experimentais foram descritas com detalhes.

3.2. Instrumentos

Foram utilizados nesta pesquisa os seguintes instrumentos: Questionário Informativo, a entrevista estruturada MINI (Mini International Neuropsychiatric Interview 5.0), o Inventário SCID II (versão brasileira: 1.0); aparelho Braintech-3000 (EMSA – Instrumentos Médicos, Brasil); o software Data Acquisition (Delphi 5.0); o joystick (Modelo Quick Shot - Crystal CS4281); o software *event-related potential (ERP) acquisition*, desenvolvido em Delphi 5.0 (Inprise Co.); a simulação tridimensional computadorizada (desenvolvida por TriptyqueLAB - www.triptyquelab.com); o programa Matlab 5.3 ® (*The Mathworks, Inc.*); e o software SPSS (versão 22.0).

3.3. Tarefa *Oddball*

A tarefa *oddball* é um método eficiente na avaliação de processamento de informação, por meio do potencial relacionado ao evento e avaliação do tempo de reação (Atagun *et al*., 2013; Schulze *et al*., 2008; Wise *et al*., 2009). Este paradigma consiste na apresentação randomizada de dois estímulos, com um deles ocorrendo de forma infrequente. Os sujeitos devem discriminar entre o estímulo-alvo (infrequente) do não-alvo (frequente). No presente estudo, optamos por utilizar um método de tarefa *oddball* visual, onde o estímulo-alvo seria apresentado na tela de um computador, por meio de um monitor de 15 polegadas. O estímulo-alvo consistia na figura de um quadrado amarelo, enquanto o estímulo não-alvo era um círculo amarelo. Os sujeitos eram instruídos a responder o mais rápido possível ao estímulo alvo, pressionando um botão do joystick (Modelo Quick Shot - Crystal CS4281). Cada estímulo era apresentado por 2.5 segundos e oscilava com a tela apagada durante o mesmo intervalo. Nós dividimos a tarefa *oddball* em quatro blocos (de 20 estímulos em cada) antes da apresentação do filme de realidade virtual e mais quatro blocos da tarefa depois de sua apresentação. O estímulo visual da tarefa foi apresentado no monitor pelo software *event-related potential (ERP) acquisition*, desenvolvido em Delphi 5.0 (Inprise Co.).

3.4. Simulação Computadorizada:

A simulação utilizada no experimento foi previamente utilizada em outros estudos, os quais confirmaram que esta é uma metodologia útil na indução da ansiedade (Freire *et al*., 2010; De Carvalho *et al*., 2013; De Carvalho *et al*., 2015). No experimento conduzido por Freire *et al*. (2010) utilizando esta simulação, em uma

amostra de 10 pacientes diagnosticados com TP, 2 tiveram ataques de pânico durante a própria atividade de realidade virtual. Esta consiste numa animação tridimensional computadorizada (desenvolvida por TriptyqueLAB) com duração de quatro minutos, os quais se dividiam na seguinte sequência: 30 segundos com a tela cinza (onde o participante permanecia em repouso), três minutos do filme e mais 30 segundos com a tela cinza. A simulação ocorre em uma perspectiva em primeira pessoa e ocorre numa sequência de fatos: início em uma parada de ônibus, o ônibus chega, o sujeito entra e se senta no ônibus, o veículo se movimenta por ruas da cidade, faz uma parada onde entram muitas pessoas, se move novamente, entra em um túnel, para dentro do túnel devido ao tráfego intenso, volta a se mover, sai do túnel, para em um ponto de ônibus, o sujeito sai do veículo e o observa enquanto se afasta (Freire *et al*., 2010; De Carvalho *et al*., 2013; De Carvalho *et al*., 2015). A simulação inclui sons relacionados com o contexto das imagens.

3.5. Procedimento experimental

Ao chegar para o experimento, cada participante preencheu um formulário informativo. Posteriormente, era orientado a se sentar em uma cadeira confortável de frente para um monitor de 15 polegadas, em uma sala com isolamento acústico, onde as luzes permaneceram apagadas durante a avaliação visando de minimizar a interferência de outros estímulos sensoriais. Com o objetivo de evitar artefatos no traçado do EEG, foi solicitado a cada participante tentasse minimizar qualquer movimento durante a captação dos sinais, como movimento de membros, aperto da mandíbula ou piscada de olhos. Inicialmente, era realizada uma captação de EEG por três minutos enquanto os sujeitos permaneciam em repouso mantendo os olhos abertos. Após isso, os participantes realizavam quatro blocos da tarefa *oddball* visual (apresentada na tela do computador) e mais um repouso de três minutos. Então era apresentado o vídeo de realidade virtual, o que somente deveria ser assistido pelos sujeitos, sem necessitarem realizar qualquer tarefa simultânea. Após o vídeo, era realizado mais um repouso de três minutos e imediatamente depois, mais quatro blocos da tarefa *oddball*. Por último, os sujeitos deveriam permanecer em repouso para a quarta e última captação em repouso durante três minutos. Desta forma, foram captados os sinais durante quatro blocos da tarefa *oddball* antes do estímulo de realidade virtual e mais quatro blocos após a apresentação deste. E no total, foram captados os sinais de quatro momentos em repouso de três minutos. O experimento foi realizado em uma só visita.

3.6. Aquisição de dados eletroencefalográficos

O aparelho Braintech-3000 (EMSA – Instrumentos Médicos, Brasil), um sistema de EEG de 20 canais, foi utilizado em conformidade com o sistema internacional 10/20 (Jasper, 1958) em uma touca de lycra (*EletroCap Inc., Fairfax, VA*) que foi ajustada individualmente em cada paciente, conforme a circunferência craniana e proporção da anatomia individual. Esta é uma montagem de vinte derivações monopolares (sendo o eletrodo Fpz utilizado como terra). O sinal referente a cada derivação EEG resulta da diferença de potencial elétrico entre cada eletrodo e a referência preestabelecida (orelhas). Foi utilizado o software Data Acquisition (Delphi 5.0), desenvolvido pelo Laboratório de Mapeamento Cerebral e Intregração Sensoriomotora. Sua configuração utiliza filtragem digital *Notch* de 60hz e filtros passa-alta de 0.1Hz e passa-baixa de 100Hz. As épocas foram recortadas de acordo com a aparição do estímulo, ou seja, 0,5 segundos antes e 1,5 segundos após os estímulos. Como apareceram 20 estímulos alvo, para cada sujeito existiram 160 épocas. Artefatos visuais foram inspecionados através de um programa de visualização utilizando o programa Matlab 5.3 ® (*The Mathworks, Inc.)* e, posteriormente, foram descartados os dados com sinais de artefatos. Foram rejeitadas, em média, 8,3 épocas por sujeito.

Devido às diferentes variáveis empregadas nos estudos, o processamento dos dados e as análises estatísticas estão detalhados nos artigos inseridos dentro do Capítulo IV.

Capítulo IV – Resultados:

Serão apresentados três artigos que foram desenvolvidos durante o programa de mestrado. O primeiro consiste em uma revisão sistemática e já foi publicado, enquanto os dois seguintes foram escritos a partir de uma pesquisa experimental que envolveu a tarefa *oddball* e a técnica de realidade virtual, os quais ainda encontram-se em fase de submissão.

O primeiro estudo, intitulado ***Evoked Potential in Panic Disorder Patients: A Systematic Review,*** teve como objetivo verificar os resultados de artigos experimentais já publicados que investigaram o componente P300 em indivíduos com TP para analisar possíveis diferenças no processamento de informações entre pacientes diagnosticados e indivíduos saudáveis. As revisões foram feitas nas bases de dados *PubMed* e *Institute for Scientific Information* e foram encontrados sete artigos que estavam em conformidade com os critérios de inclusão e exclusão que foram escolhidos. Os resultados apontaram que indivíduos com TP apresentaram prejuízo no processamento de informações e na atenção, assim como apresentaram inabilidade nas respostas automáticas a novos estímulos e prejuízo na interpretação de estímulos internos e externos relacionados com o transtorno.

No segundo estudo, denominado ***How high level of anxiety in Panic Disorder can interfere in working memory? A virtual reality and electrophysiological investigation***, utilizamos a função de coerência do Eletroencefalograma quantitativo para investigar diferenças entre pacientes com TP e indivíduos saudáveis na banda gama, a qual foi observada durante a execução da tarefa *oddball* realizada antes e depois a apresentação de um filme de realidade virtual com estímulos ansiogênicos, tendo como objetivo analisar se altos níveis de ansiedade (produzidos pelo filme de realidade virtual) poderiam afetar a memória de trabalho. Uma ANOVA *two-way* foi aplicada para a análise estatística dos fatores grupo e momento separadamente para cada par de eletrodos, e outra para analisar a variável tempo de reação. Um $p \leq 0,05$ foi considerado estatisticamente significativo e os resultados demonstraram efeito principal para os fatores grupo e momento. Verificamos um aumento da coerência em gama no par de eletrodos F3-P3 após o filme, demonstrando uma participação do hemisfério esquerdo sobre o processamento da ansiedade. A maior coerência em gama observada nos controles saudáveis sobre as áreas frontal e parietal (P3-Pz, F4-F8 e Fp2-F4) aponta para a participação destas áreas com o comportamento esperado. Já o aumento da

coerência em gama observada em pacientes nos pares de eletrodos F7-F3 e F4-P4 apontam para um "ruído" prejudicial sobre o processamento de informações, que pode ser associado à uma interferência na comunicação entre áreas cerebrais. Tais resultados estão de acordo com diversos sintomas do TP.

Já no terceiro artigo, intitulado ***A virtual reality and electrophysiological investigation in panic disorder patients during the oddball paradigm***, utilizamos a mesma metodologia do segundo artigo para analisar possíveis alterações no processamento de informações em pacientes com TP, mas desta vez utilizando a medida potência absoluta da banda alfa (8–13 Hz), devido à relação desta oscilação eletrofisiológica com processos *top-down* e de controle inibitório. O objetivo deste estudo era verificar possíveis diferenças na potência absoluta de alfa entre pacientes com TP e controles saudáveis, assim como verificar a interferência da ansiedade desencadeada pelo filme na potência absoluta de alfa. Na análise estatística, foi aplicada uma ANOVA *two-way* para analisar os fatores grupo e momento para cada eletrodo separadamente e outra para a variável tempo de reação. Nos resultados, foi constatada uma diminuição na potência absoluta de alfa nos pacientes com TP durante a tarefa *oddball*, além da observação de uma diferença significativa entre os quatro momentos analisados, onde a potência absoluta de alfa aumentava com o avanço dos momentos. Outro dado importante foi a análise comportamental do tempo de reação, que apontou que pacientes com TP foram mais rápidos que participantes saudáveis, o que pode estar relacionado com uma maior excitabilidade e reatividade aos sintomas característicos do TP.

4.1. Artigo I: **Evoked Potential in Panic Disorder Patients: A Systematic Review**

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Evoked Potential in Panic Disorder Patients: A Systematic Review

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Abstract: Researchers have been using the electroencephalogram to better understand the cognitive and neurobiological bases of panic disorder (PD) through the P300 component; this is an electric potential of the cerebral cortex that is generated in response to external sensorial stimuli and which involves more complex neurophysiological processes related to stimulus interpretation; it is then used to investigate possible alterations in the information processing and attention of patients suffering from this disorder. Aiming to verify the results found by experimental articles already published about P300 in PD patients and the information processing differences between PD patients and healthy controls, a systematic review of the PubMed and Institute for Scientific Information databases was conducted. The selection criterion involved those articles, written in English, which referred to an experimental research that focused on the P300 component, with a sample composed of PD (or panic attacks) patients. Seven articles were found that fit the selected criteria. Most of the articles show that these patients suffer from: impaired information processing and attention, an inability to automatically respond to new stimuli, and impaired interpretation of internal and external stimuli related to the disorder. Such impairment may be related to an unspecified dysfunction in the limbic-reticular structures, which would affect: active, focused and short-term attention, working and short-term memory, recognition and decision making. Some limitations were highlighted, such as the use of small samples and possible comorbidity with other disorders, which did not

allow clearer results. This research can contribute to understand the neurobiological differences of PD patients and develop treatments based on such evidence.

Keywords: Electroencephalogram, neurobiology, P300, panic disorder.

INTRODUCTION

Panic Disorder (PD) is a psychiatric disorder highly prevalent in society [1] and greatly impacting the quality of life of those who suffer from it [2]. Due to this condition, the patient suffers from repeated and unexpected bouts of intense anxiety, which are not restricted to a determined situation or circumstance, and which can comprise: the fear of death, the fear of losing control and going insane, depersonalization, derealization, chest pain and/or discomfort, palpitations and tachycardia, breathlessness, asphyxia, transpiration, dizziness, high body temperature, and others [3]. PD is predominant in women and its frequency and course are variable. Agoraphobia, which is commonly associated with PD, is connected with the anxiety related to specific places or situations, which end up being avoided [3]. In the last year, studies on PD were conducted for a better understanding of its neurobiological base, as well as of the psychophysiological, cognitive and behavioral functioning involved in this psychopathology.

The cognitive basis of PD originates from the dysfunctional interpretation of bodily sensations [4] and an inadequate processing (of "catastrophizing") of the information coming from an external stimulus [5]. Thus, according to the cognitive model of PD, the stimulus interpretation that is understood as dangerous generates apprehension, which sets off the sympathetic activation and consequent bodily sensations. These signs are then interpreted as "confirmation of danger", therefore producing an even stronger anxiety [6].

The neurobiological hypotheses of PD are coherent with the cognitive processing hypotheses, since many researchers attribute anxiety to a dysfunctional interaction between the pre-frontal cortex and the limbic system [7]. The pre-frontal cortex is related to: executive function, cognitive flexibility, working memory [8], behavioral planning and complex thoughts, like decision making, attention control [9, 10], behavior modulation [7, 11], emotional regulation [7, 12]. Limbic-reticular structures play an important role in the formation of emotionally motivated behavior, in

short-term memory, and in cognitive functions, such as recognition and differentiation [13]. The limbic system and the pre-frontal cortex are mutually connected, thus the individuals can also exert control over their emotional state [14], and mediate the conditioning of fear by an unconscious detection of threat [7]. With the objective of investigating the cognitive and neurobiological aspects of anxiety disorders, researchers have been using the electroencephalogram (EEG) to observe the information processing of anxiety patients, and among them, those with PD, through the event-related potential (ERP).

ERP is the name given to the electric potential of the cerebral cortex that is generated in response to external sensorial stimuli. There are four different types of ERP: auditive, visual, sensorial and cognitive. In this study, we will focus on the cognitive type, the P300, named so, for its occurrence around 300ms after the stimulus. These are long latency potentials, caused by environmental stimuli, and they involve more complex neurophysiological processes related to stimulus interpretation, such as memory, expectation, and attention, among others. They have been discussed as indicators of the level of processing and storage of memory [5, 15]. The empirical and theoretical knowledge suggests that P300 can come from inhibitive neuronal activity, which enhances attention focus, to promote memory storage [16].

The ERP analysis started being used with the objective of studying cognitive functions in the 1960s, and is currently being used in neurological practice. Published data point out P300 as a complex heterogeneous wave that serves as an electrophysiological correlation between emotions and cognitive processes [17]. Several researchers correlate changes in the amplitude of P300 with changes in the level of attention, indicating this as being directly proportional to the level of attention in task execution [17]. Specifically, the P300 peak is considered as a measurement of the individual attention level. The amplitude of P300 is significantly influenced by the complexity of a stimulus, while the latency of P300 is directly connected to the speed at which the task is executed.

P300 can be observed through the variation of amplitude of mid-line electrodes (Fz, Cz, Pz), which increases from the frontal to the parietal electrodes, in the presence of target stimuli. The structures involved in the generation of P300 are the hippocampus, the temporal, frontal and parietal lobes, the cingulate cortex and subcortical areas, such as unspecified thalamic nuclei and reticular formation of the

cerebral trunk. These structures form emotional and motivational behavior, as well as cognitive functions. These areas are also related to the pathogenesis of PD [17].

Changes in the P300 parameters can be observed in patients with cognitive alterations and anxiety disorders. While several studies have demonstrated that a smaller latency period and larger amplitudes were typical of subjects with better cognitive abilities, others pointed out that there is a relationship between changes in amplitude time, typical of the P300 wave, and the severity of cognitive impairment [17].

Convergent empirical data obtained through clinical observation, behavioral data and psychophysiological studies suggest that subjects with PD, with or without agoraphobia, exhibit a poorly adaptive development of attention, secondarily to sensorial information processing disorders. Behavioral data point out that subjects with PD maintain an excess of self-focused attention and worry about distorted thoughts and images, while demonstrating, at the same time, a reduction in the attention to the external environment [18].

Starting from the hypothesis that PD patients suffer from impaired information processing and, consequently, show significant differences in ERP, a systematic review was conducted, with the objective of verifying the literature about P300 in PD (or panic attacks) patients, in order to better understand the differences of information processing between PD patients and healthy controls (HC) and research whether such cognitive function is or not impaired by this disorder.

METHODOLOGY

A systematic review of the PubMed and Institute for Scientific Information databases was conducted on July 27, 2014, inputting the following expressions: “evoked potential” and “panic disorder”, “evoked potentials” and “panic disorder” (62 articles were found); "P300" and "panic disorder" (15 articles were found); "P3" and "panic disorder" (11 articles appeared).

The selection criterion utilized involved those articles, written in English, which referred to an experimental research that focused on the P300 component, with a sample composed of PD (or panic attacks) patients. Articles that appeared repeated times or that did not fit the selection criteria were discarded, leaving only seven articles available. Articles whose samples were formed by patients that reported comorbidity with any other mental disorder were also not included.

The articles are presented in a chronological order, so as to describe their objectives and methods, emphasizing the results that were found in each of the researches (Table **1**). The discussion was written after observing the points in common among the articles, such as P300 amplitude, its latency, the P3a component analysis and the cognitive aspect of PD, in order to examine their results and answer the hypotheses of this research.

RESULTS

In order to investigate the ERP indexes of information processing in PD patients, Clark and collaborators [19] utilized the EEG to scan the activity of patients (n=14) e HC (n=15), in a task where they had to differentiate infrequent target-sounds from frequent and infrequent distractive sounds, pressing a lever when recognizing the target-sounds. The study analyzed the activity of three electrodes: Fz, Cz and Pz. It was observed that P300 was greater in target sounds that in distractive-sounds, except for the Cz electrode, on which P300 was greater for distractive-sounds than for target ones. P300 appeared first in the front-central areas for target-stimuli, while P300 amplitude in the presence of target- and distractive-sounds was significantly greater in PD patients. In the presence of infrequent stimuli, patients demonstrated an increase in the front-central P300; according to the author, this result suggests that PD involves an abnormality in the P3a component, which is observed in the presence of new stimuli. The P3a component is a frontal or central P300, with short latency and quick habituation, and is interpreted as a reflex of the frontal and hippocampal activity [16]. The results of this study show greater P3a in PD, which indicates an abnormal response from those cognitive processes that occur automatically when facing a new situation or change of stimulus [19].

Study	Subjects (n)	M/F	Age (Average ± DP)	Visual	Auditory	Scales	Results	Commentaries	Ref.
Clark *et al*. (1996)	14 P 15 C	0/8 0/8	36.9 ± 12.4 years 31.0 ± 10.5 years		X	NART, GHQ, SDS, STAI.	Raised frontocentral P300 and P3a on PD, what indicates an abnormal response of cognitive processes to new stimuli.	Psychological evidence of impaired abilities to filter new stimuli. Hyperactivity of the pre-frontal and limbic ways.	[19]
Iwanami *et al*. (1997)	12 P 12 C	6/6 7/5	34.4 ± 9.0 years 35.6 ± 9.9 years		X	STAI e MAS.	P300 component was elicited in response to the target-stimulus in the patient group as well as the control group. There was no significant difference between patients and controls in P300 amplitude and latency	Preservation of controlled processes involved in information processing, with no compromise, impairment or facilitation	[20]
Pauli *et al*. (1997)	15 P 15 C	4/11 4/11	35.5 average 35.3 average	X			Higher P300 amplitudes in response to the presentation of words related to bodily sensations.	The behavioral and electrophysiological findings show that PD patients perceive and process the stimulus related to bodily sensations, especially the one related to anxiety and excitement, in a catastrophic way.	[5]
Gordeev (2003)	42 P 23 C	14/28 8/15	30.5 average 29 average		X	BDI, STAI, TAS, ST, MT.	Decreased P300 amplitude and differences in the habituation in both hemispheres on PD patients.	The results appoints to a non-specific dysfunction in the limbic-reticular structures.	[13]
Gordeev (2008a)	77 P 28 C	24/53 9/19	31.6 ± 3.1 years 30.7 ± 2.5 years		X	BDI, ST, TAS, MT.	P300 peak significantly smaller in PA patients with agoraphobia than those without agoraphobia. Difference in the process of habituation.	Impairment in active and focused attention and in short-term memory of PA patients.	[22]
Gordeev (2008b)	93 P 36 C	30/63 12/24	31.2 ± 1.2 years 30.1 ± 1.2 years		X	BDI, STAI, MT, ST and short-term memory testing with words and numbers.	Reduction of P300 amplitude on atypical PA atypical, and raised amplitude on typical PA, witch showed high levels of anxiety	Functional impairment of the temporal limbic-reticular structures in PA patients. The main factor in the pathogenesis of cognitive disorders in PA patients seems to be the presence of accentuated anxiety and depressive disorder.	[17]
Wise *et al*. (2009)	50 P 98 C	15/35 29/69	35.8 ± 13.36 years 35.56 ± 13.05 years		X		Reduction on P300 amplitude and short latency on target stimuli. Increased amplitude on frequent or irrelevant stimuli.	PD patients presents an inability of properly allocating neural resources to the stimulus, affecting the information processing.	[18]

NART: National Adult Reading Test (Nelson, 1982); GHQ: General Health Questionnaire (Goldberg, 1970); SDS: Self-Rating Depression Scale (Zung, 1965); MAS: Manifest Anxiety Scale (Taylor, 1953); BDI: Beck Depression Inventory; STAI: State-Trait Anxiety Inventory (Spielberger, 1983); TAS: Toronto Alexithymia Scale; ST: Schulte Tables; MT: Munsterberg Test.

The study by Iwanami and collaborators [20], whose goal was investigating the psychophysiological characteristics of PD, observed that, when facing a task where a button needed to be pressed when the patients noticed the rare target sounds, the P300 component was elicited in response to the target-stimulus in the patient group (n=12) as well as in the control group (n=12). In this research, the author reported that there was no significant difference in the P300 amplitude and latency between patients and HC. Such data, together with the absence of significant differences in the behavioral indexes of the two groups, were interpreted as an indicator of the preservation of controlled procedures involved in information processing present in PD, with no involvement, impairment or facilitation [20].

Pauli *et al*. [5] utilized a sample of 15 PD patients and 15 HC, and sought to examine the limits of the PD patients' perception about sets of words related to the disorder and to demonstrate that the cognitive tendency in the processing of stimuli related to anxiety is reflected by abnormal ERP, set off by such stimuli. Utilizing a tachyscope, patients were shown words related to bodily sensations, alternated with neutral words. Behavioral measurements (proportion of correctly recognized words) and electrocortical measurements (cerebral potentials related to events) were registered. A positive peak (P300) was observed around 300ms after the stimulus appearance, followed by a lengthy positive slow wave from 400 to 900ms. In PD patients, the slow wave was clearly more positive after words related to bodily sensations than after neutral words, showing P300 amplitudes that were significantly greater, while controls seemed not to be affected by either type of words. The author emphasized that PD patients perceive and process the stimulus related to bodily sensations, especially the one related to anxiety and excitement, in a catastrophic way [5]. The behavioral and electrophysiological findings agreed with this hypothesis, since the percentage of correct word identification and the ERP measurements of PD patients were affected depending on the type of word presented. PD patients showed an increase in the P300 amplitude and a more positive slow wave in the periods between 400 and 500ms and 600 and 800ms, in response to the appearance of a word related to bodily reactions. The author mentioned that such data is in agreement with other studies, that show that affective stimuli, if compared to neutral stimuli, cause an increase in the late positive slow wave [5, 21].

The researcher Gordeev has published three studies that mentioned the P300 component and PD. In the first one of those studies, Gordeev [13] detected P300 to

research the hypothesis that the decrease of P300 amplitude would reflect an increase in the activity of the cerebral reticulo-thalamic structures, while an increase in amplitude would be related to the hyperactivity of the septo-hippocampal limbic system in PD patients. The utilized method consisted in the presentation of an auditive stimulus, through which a rare stimulus (target) and a frequent stimulus (non-target) were also presented to PD patients (n=42) and HC (n=23). The habituation was evaluated by comparing amplitudes of successive P300 blocks, consisting of 2 to 3 cycles. Besides that, psychometric tests were used: Beck Depression Inventory (BDI), Spielberger's State-trait Anxiety Inventory (STAI), Toronto Alexithymia Scale Schulte tables (ST), Münsterber Test (MT) and Autonomic Inventory and Hyperventilation Questionnaire. A decrease in P300 amplitude was found and differences in the habituation in both hemispheres were also found in PD patients. The results suggest that changes in the P300 amplitude of PD patients reflect a non-specific dysfunction in the limbic-reticular structures. The data from the electrophysiological studies were related to the psychometric test results, indicating high anxiety, distractibility, depression, and disturbances in the selectivity and stability of attention in PD patients, when compared to the controls [13]. In that same study, patients were divided into two subgroups, according to the results. Subgroup 1 included those subjects who showed low P300 amplitude, disturbances in their habituation and disorder in selectivity and direction of attention (compared to the HC and subgroup 2). Meanwhile, subgroup 2 was composed of those subjects that exhibited a higher P300 amplitude (compared to the HC and subgroup 1) and slower habituation, though not distorted. The decrease in the P300 amplitude in subgroup 1 can be explained by the high activation of non-specific reticulo-thalamic structures of the brain [13], which can also be observed through the decrease in the alpha band, the increase in the activity of the beta band and the decrease of amplitude in the contingent negative variation. The habituation unbalance of this group may indicate a predominance of activating processes [13].

In his second article [22], Gordeev analyzed cognitive functions in an objective way, starting with the evaluation of the P300 component in the presence of random events, according to the *oddball* paradigm. For this reason, he utilized auditive stimulation with separate triggers for the initial stimulus and the rare (target) stimulus. The sample was composed of 77 patients with frequent panic attacks (PA), and 28 HC. The analysis was conducted utilizing a neurological clinical investigation, besides the use of psychometric instruments (BDI, STAI, Toronto Alexithymia Scale, ST and MT).

P300 amplitude was found to be lower for the patient group, impaired P300 habituation was also observed in both hemispheres. However, patients suffering from agoraphobia showed a P300 amplitude peak significantly lower than those without agoraphobia, as well as a difference in the habituation process. While patients who did not suffer from agoraphobia demonstrated a plunge in the amplitude between the first and second cycles, agoraphobic patients demonstrated an increase in the peak of the amplitude when the subsequent stimuli blocks appeared. It was observed that P300 amplitude is directly proportional to the level of attention to the task at hand, and that it also depends on the working memory capacity. When short-term and working memory capacities decrease, the period of latency of the P300 component increases [22]. The author concluded that the low P300 amplitude in PA patients can be the evidence of an impairment they suffer in their active and focused attention and in short-term memory. While the HC showed a decrease in the period of latency and in the P300 amplitude after any attempt, the patients showed a greater P300 amplitude peak, compared to the first attempt. Thus, PA and agoraphobia patients seem to be characterized by a predominant activation of the ascending mesencephalic reticular formation, which is related to the high levels of endogenous and reactive anxiety [22]. Patients without agoraphobia seem to exhibit a significant increase in the temporal-limbic structures. Thus, agoraphobic patients show a lower P300 amplitude peak, significantly impaired P300 habituation, highly impaired attention and more elevated levels of anxiety and depression, when compared to those subjects without agoraphobia [22].

In his third article, Gordeev [17] aimed at running a psychophysiological study of the cognitive functions and the functional state of non-specific cerebral systems in typical or atypical PA patients. He classified as typical symptoms of PA: the sensation of breathlessness or difficulty to breathe, strong palpitations or pulsations all over the body, transpiration, limb paresthesia, cold or heat sensations, shivering and goose bumps, the feeling that the world is not real, vertigo and instability when walking, pre-syncope feeling, fear of death, interior tension, fear of “losing one’s mind” or performing uncontrolled deeds. Among the atypical symptoms one would find: feeling a lump in the throat, limb convulsion, unpleasant sensations in the stomach or intestine, greater intensity of sight or hearing, feeling of weakness in the hands or feet, voice or speech loss, the feeling that one’s body has been stretched, loss of consciousness, anger or irritability and headache. The method utilized in this research consisted of a clinical and neurological investigation (computerized tomography, magnetic resonance imaging

and EEG), psychometric testing (STAI and BDI), neuropsychological studies (MT, ST and short-term memory testing through words and numbers) and neurophysiological studies (ERP with evaluation of P300) with PA patients (n=93) and HC (n=36). The investigation pointed out a decrease in the P300 amplitude peak, with atypical PA, when compared to HC; according to the author, this is mainly associated with impaired cognitive functions in such patients (decrease in short-term memory, impaired attention selectivity, change and stability processes), due to high levels of anxiety and depression, which can also be associated with all this. On the other hand, typical PA patients demonstrated an increase in the P300 amplitude. Typical PA patients, compared to atypical PA patients, demonstrated significantly higher levels of anxiety and depression and more accentuated cognitive impairments, in areas such as attention and memory.

According to the author, the changes in amplitude characteristic of the P300 peak seen in the study can serve as an objective neurophysiological measurement for the cognitive and emotional impairments, due to a functional impairment of the temporal limbic-reticular structures in PA patients. The dysfunction in these structures is also indicated by neurophysiological testing, which suggested the evidence of impaired processes of attention selectivity, change and stability, and a decrease in short-term memory in this group of patients. The degree of cognitive impairment increased, in both groups of patients, as the levels of depression and anxiety increased as well. For Gordeev [17], this can lead to the conclusion that the main factor in the pathogenesis of cognitive disorders in PA patients seems to be the presence of accentuated anxiety and depressive disorder, characterized by high distractibility, difficulty to execute tasks and low motivation [17].

In the last selected article, Wise *et al*. [18] investigated the information process in PD, utilizing the *oddball* paradigm to observe the patients' response to target and distractive auditive signs. The sample was composed of 50 PD patients and 98 HC. When exposed to infrequent stimuli, the patients demonstrated: decreased P300 amplitude (especially for the Cz and Pz electrodes), reduced latency (especially for the Fz, Cz and Pz electrodes), increase in heart beat rate and less spontaneous skin conductivity. When frequent stimuli appeared, P300 amplitude increased. Results suggest an inability to properly allocate neural resources to the stimulus, therefore affecting the information processing, since patients showed difficulty in discriminating the auditive stimuli in the context of a very simple task of auditive discrimination. This

data reflect the reduced adaptive flexibility of multiple levels of functioning, such as autonomic, perceptual, behavioral, affective, cognitive and cortical levels [20].

DISCUSSION

The article review showed that the P300 amplitude and latency are aspects that are being studied to better understand the information processing of PD patients. Besides this, the studies also reported how anxiety affects the information processing [7, 13, 17, 19, 22, 23].

With regards to the investigations related to the P300 amplitude, only one article did not find any amplitude or latency difference between PD patients and controls. Iwanami *et al*. [20] attributed this similarity to the preservation of the procedures responsible for information processing. Therefore, PD patients would not suffer from impaired information processing.

In contrast, Pauli and collaborators [5] observed that PD patients presented greater amplitudes than the controls, in the presence of stimuli related to the disorder, such as bodily sensations and anxiety. This study has shown that PD patients have a low perceptual threshold to words related to bodily sensations and that the correct recognition of those words is associated with a slow wave increase in those patients.

Several authors have observed a P300 amplitude increase in patients with different signs of anxiety (such as obsessive compulsive disorder and panic attacks), when compared to controls, and have interpreted this increase as a sign of cortical neuron hyperactivity, reflecting a deficit in cognitive functions, such as memory and directed attention [17, 24, 25]. The greater amplitude and slower habituation can indicate hyperactivity of the septo-hippocampal limbic structures, and can be confirmed by the increase in the s pectral potency of the EEG for theta waves in some PD patients [13].

Emotional tension decreases the ability of redistributing and changing attention, as well as changing its level. Such characteristics of a concentration decrease are typical of anxiety. Studies associate the P300 amplitude peak increase with a betterment of attention, counting and logical functions of memory [26]. However, other neuropsychological studies indicate that the P300 component with a smaller latency period and larger amplitude is typical of subjects with better cognitive abilities [27].

Disagreeing with the results described above, four of the seven articles pointed out the P300 amplitude decrease in PD patients. As found in the three studies by Gordeev [13, 17, 22], the smaller amplitude and impaired habituation of anxious patients was related to impairments in the active, focused attention and short-term memory, which was also evidenced in the results from the neuropsychological tests. The P300 amplitude peak decrease, mostly highlighted in PA and agoraphobia patients, when compared to patients without agoraphobia, is related to impairments in attention selectivity, redirectioning, stability and concentration [22]. Wise [18] interpreted the amplitude and latency decrease in PD patients as an inability of properly allocating neural resources to the stimulus, therefore affecting the information processing. According to this author, the combination of decreased amplitude and latency suggests that the processing of the environmental signs in these patients is accelerated and impoverished. The pattern of impairment in the processing of stimuli can contribute to the excessive reactivity of patients in places with a high sensorial load, for they have an excessive non-adaptable focus on those stimuli related to the disorder, such as bodily sensations [18].

Such amplitude change points out a non-specific dysfunction in the limbic-reticular structures, which play an important role in the formation of motivating behavior, short-term memory and cognitive functions such as recognition, differentiation and decision making [13]. In addition to this, the reticular formation located in the cerebral trunk is responsible for the regulation of the state of alertness and for subsiding the attention process [28]. Thus, due to such dysfunction, patients consequently feature impairments in the active, focused and short-term attention. This data was confirmed thanks to the neuropsychological scales employed, which also indicated distractibility and disturbances in attention selectivity and stability. Even though P300 is considered a biologic milestone for cognitive capability deficits in PD patients [29], the significant heterogeneity and possible comorbidities present in PD make it difficult to detect specific deficits using P300 [18, 29].

A decrease in amplitude seems to be present in affective and psychotic phenotypes [30-32], and it can be related to possible impairments on emotion's cortical control, resulting in high reactivity to environments of high emotional significance [18, 19, 32]. According to De Carvalho *et al*. [33], the pathophysiology of PD is considered to be heterogeneous and it involves limbic, cortical and subcortical regions. The most

common electrophysiological differences between HC and PD patients are found in the frontal and parietal cortexes [34].

Clark *et al*. [19] evaluated the P3a component; P3a is understood as a reflex of frontal and hippocampal activity [16]. P3a and P3b are proposed to result from the operation of inhibitory mechanisms engaged by incoming stimulus events to facilitate memory processing [52]. According to Polish [16], P3a is a positive wave with a maximum distribution of amplitude that is found in the central and parietal regions. These components are elicited by an infrequent distracter stimulus, randomly inserted into the target/standard sequence. This potential has been called the "novelty P300". P3a amplitude decreases when the stimulus is presented repeatedly. P3a results from a process related to initial and focal attention, which occurs thanks to a representational change in the working memory, and is mediated by the dopaminergic activity [16].

The P3a component appears when a signal of the stimulus is transmitted, due to the attention activation resources, which promote memory operations in the temporal and parietal areas [16, 35]. This component is associated with the norepinephrine system [16, 36, 37]. The evaluation of the stimulus involves focal attention (P3a) to ease the maintenance of representational context (P3b), which is related to context updating operations and subsequent memory operations and storage [16, 38, 39]. The context updating approach may reflect relatively strong initial target stimulus processing, which is more related to P3a, and diminishes as the repeated target stimuli occur, in order to produce the P3b [39, 52].

Clark *et al*. [19] observed greater P3a amplitude in PD patients, which, according to the author, would indicate an abnormal response of automatic cognitive processes to new stimuli and could explain the reason why PD patients are excessively excited in environments rich in irrelevant stimuli, like crowded places or supermarkets. The author even affirms that the P3a abnormality in PD is most likely related to a hyperactivity of the pre-frontal and limbic ways.

The increase of P3a in the presence of irrelevant stimuli is characteristic of the activity that is expected in reaction to new or irrelevant events, and is consistent with the functional pathology involving the pre-frontal and limbic ways. This study has presented psychophysiological evidence of an accentuated disorder in PD, characterized by an impaired ability of filtering the stimulus, based on the novelty of this stimulus [4, 19]. Clark *et al*. [19] also pointed out that, usually, P3a habituation occurs after the presentation of repeated stimuli, but indicated that habituation may decrease in PD.

Abnormalities in habituation of the P300 amplitude peak were observed in the three studies conducted by Gordeev [13, 17, 22]. While healthy people demonstrated a decrease in the latency period and P300 amplitude after repeated appearances of a stimulus, PD and agoraphobia patients might demonstrate an increase in P300 amplitude after the first appearance of the stimulus, what Gordeev [22] classified as "de-habituation" or "distortion of habituation". More significant habituation impairment in these patients can reflect more significant anxious and depressive disorders, if compared to patients without agoraphobia [17]. The slower habituation can be possible evidence of activator processes related to the possible increase of mesencephalic reticular formation activity [17].

Considering that there is an inadequate information processing of external stimuli in PD patients [4, 6, 40], the studies related above highlighted that the cognitive model of such disorder must be considered, in a way so as to complement the understanding already existent about its biological basis. According to the cognitive-behavioral models, panic attacks can origin from distorted and catastrophic interpretations of bodily symptoms [4]. These interpretations enhance the excitement and intensify the bodily sensations, confirming, thus, a sense of imminent "danger", elevating the level of anxiety and generating more catastrophic interpretations in a rapid spiral. According to Barlow [41], an initial panic attack represents a "false alarm" in which too much anxiety is signalized, usually in response to the stress of life.

Authors have worked with the hypothesis that the repetition of attacks can make individuals progressively more sensitive to internal stimuli and to the situations in which the attack has occurred and that enhances the watchfulness over a physical sensation. Combined to that, there is anticipatory anxiety, that is, the fear of suffering another attack, and the catastrophic interpretations of the symptoms when they occur [42, 43].

Pauli [5] has shown that, after being in the presence of stimuli related to bodily sensations, patients presented slightly greater P300 amplitudes, indicating that these patients process these sensations in an affective or catastrophic way. As it has already been stated, the data of this research reveal that PD patients possess a low perceptual threshold to words related to bodily sensations, which affects the correct recognition of those words. These results are in agreement with the cognitive model of PD, which points out that the patient interprets the information (or bodily sensations) in a catastrophic way and, consequently, suffers an increase in anxiety. In agreement with

such result, Wise *et al*. [18] indicated that PD patients demonstrate a reduced ability of properly attributing significance to the stimulus, whether it be internal or external, which results in an inappropriate attribution of the attention processing resources. This understanding contrasts the research conducted by Windmann *et al*. [7], who observed that words with a negative emotional connotation did not influence PD patients, interpreting this as evidence for a dysfunctional inhibitory modulation of the affective information processing in PD patients.

According to Pauli *et al*. [25], cognitive bias (or cognitive distortions) in anxiety disorders seem to be automatic, having effects that seem to be involuntary and unconscious. In anxiety disorders, the initial process – which occurs when the stimuli do not need to be analyzed completely to be selected – can be faster, involuntary, inflexible, pre-attentional and driven by the stimulus, while the late process – which occurs when the sensorial stimuli pass through a pre-analysis of characteristics and signification and, only later, the selected stimuli reach a state of processing that is more complex [44] – can be slow, dependent on effort, driven by schemes and conscious [45]. Thus, anxious patients may be incapable of inhibiting responses to the initial automatic fears and/or improving these responses through strategic late processes [45]. These responses might be related to deficits in conceptual verification or pre-attentional inhibition, set off by ascending alarm signals starting from diencephalic structures of the limbic system [7, 19, 45, 46].

Some methodological aspects that were evidenced in this systematic review must be considered for future investigations. The presence of small samples and possible comorbidity with other disorders did not allow clearer results. Besides this, due to existence of different methods of EEG signal analysis, it is difficult to chart the results found in a more conclusive way, since there is no consensus about the main electrophysiological alterations in PD [47-52].

CONCLUSION

As it was reported, P300 can reflect fundamental indexes of attention and operations related to memory. In most of the analyzed researches, PD patients demonstrated impaired information processing, since they showed a decreased P300 amplitude and latency. This can be related to a non-specific dysfunction in the limbic-reticular structures, which would affect active, focused and short-term attention,

working and short-term memory, recognition and decision making. This data highlight an inability of the automatic cognitive processes to respond to new stimuli, therefore contributing to the excessive reactivity in environments rich in irrelevant stimuli or with high sensitive load, since they encourage an excessive focus on those stimuli related to the disorder, such as bodily sensations or crowded places.

PD patients were characterized as possibly making an inadequate interpretation of internal (bodily sensations) and external (environmental) stimuli as dangerous and catastrophic, which could be related to a failure to automatically inhibit responses to fear, or failure in the modulation of more sophisticated and conscious responses.

There is still much to be researched in the area of electrophysiology about anxiety disorders, therefore, future researches should attempt to observe and understand not only the neurobiological differences between PD patients and HC, but also the difference between the results that were found before and after the treatments with cognitive behavioral therapy and/or medicament treatment.

LIST OF ABBREVIATIONS

BDI = Beck Depression Inventory

EEG = Electroencephalogram

ERP = Event-Related Potential

HC = Healthy Controls

MT = Münsterber Test

PD = Panic Disorder

ST = Schulte Tables

STAI = Spielberger's State-trait Anxiety Inventory

CONFLICT OF INTEREST

The authors and the represented institutions confirm that the content of the present article has no conflict of interest.

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4.2. Artigo II: **How high level of anxiety in Panic Disorder can interfere in working memory? A computer simulation and electrophysiological investigation.**

How high level of anxiety in Panic Disorder can interfere in working memory? A computer simulation and electrophysiological investigation.

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Abstract:

Panic disorder (PD) is characterized by repeated and unexpected attacks of intense anxiety, which are not restricted to a determined situation or circumstance. The coherence function has been used to investigate the communication among brain structures through the quantitative EEG (qEEG). The objective of this study is to analyze if there is a difference in frontoparietal gamma coherence (GC) between panic disorder patients (PDP) and healthy controls (HC) during the Visual oddball paradigm; and verify if high levels of anxiety (produced by a

computer simulation) affect PDP's working memory. Nine PDP (9 female with average age of 48.8, SD: 11.16) and ten HC (1 male and 9 female with average age of 38.2, SD: 13.69) were enrolled in this study. The subjects performed the visual oddball paradigm simultaneously to the EEG record before and after the presentation of computer simulation (CS). A two-way ANOVA was applied to analyze the factors Group and the Moment for each pair of electrodes separately, and another one to analyze the reaction time variable. We verified a F3-P3 GC increased after the CS movie, demonstrating the left hemisphere participation during the anxiety processing. The greater GC in HC observed in the frontal and parietal areas (P3-Pz, F4-F8 and Fp2-F4) points to the participation of these areas with the expected behavior. The greater GC in PDP for F7-F3 and F4-P4 pairs of electrodes assumes that it produces a prejudicial "noise" during information processing, and can be associated to interference on the communication between frontal and parietal areas. This "noise" during information processing is related to PD symptoms, which should be better known in order to develop effective treatment strategies.

Key words: Panic disorder – EEG – Gamma coherence - Information Processing – working memory.

Introduction:

Panic disorder (PD) is an anxiety disorder with a high prevalence in society [1,2,3]. The intense frequent symptoms can impact the quality of life, even causing professional and social difficulties or incapacitation. Patients diagnosed with PD suffers from repeated and unexpected attacks of intense anxiety, which are not restricted to a determined situation or circumstance. The attacks can result in fear of death, fear of losing control, dizziness, palpitations and tachycardia, breathlessness, asphyxia, and others [3,4,5]. In this context, PD and its cognitive, behavioral and neurobiological bases have been widely investigated in the last couple of years.

The cognitive model of PD explains that there is an inadequate and dysfunctional processing of external stimuli and bodily sensations in these patients [3,4, 6-8]. They misinterpret some environment or bodily stimuli as signs of danger, setting

off the sympathetic activation and consequent bodily sensations of anxiety. These uncomfortable sensations are misinterpreted as confirmation of the danger potential of stimuli or situation, which can produce even stronger anxiety [3,7]. This vicious cycle then presumably induces panic attacks. Neurobiological hypotheses and cognitive processing hypotheses both attribute the PD anxiety to a dysfunctional interaction between the pre-frontal cortex and the limbic system [9].

These hypotheses led many researchers to investigate what were the cognitive deficits related to PD. Mixed results were reported in relation to working memory and PD. Although many research studies showed that patients with PD do not present impairments in working memory [10,11], others subscribe results that points to deficit in this cognitive ability. This impairment can be related to difficulties in the information processing and, consequently, to the misinterpretation of bodily symptoms. In the study conducted by Dratcu and Bond [12], patients with PD presented impairments of both working memory and explicit memory. The authors explained that such deficits may be related to a high level of excitement and anxiety in patients during the task execution. The post-traumatic stress disorder study conducted by Clark et al. [13] shows that these patients present a quite different electrophysiological profile, with indicators of both an abnormal fear response and disrupted information processing mechanisms relevant to attentional focus during working memory operations.

In this context, CS movies and virtual reality are techniques that have been used as an important tool to investigate neurobiological parameters. According to Kalckert [14], virtual reality is an elegant method as it allows perfectly aligning the apparent (visual) position and proprioceptive position of the participant. CS can induce anxiety in patients with PD and agoraphobia [15] in an environment fully controllable by the investigator [16]; and also has been used in research with anxious patients and as a treatment tool of psychotherapy [17]. To explore the effects on human brain cognitive functions after the exposure to the CS, we used the quantitative electroencephalography (qEEG) functional network analysis methods to examine topological changes in the connection of cognitive regions [17-20]. It is a useful tool to extract the indicators of cognitive load in real-time [21]. Research studies have been using the qEEG to investigate the communication among brain structures through the coherence function. This function analyzes how much two brain networks are functioning with similarity, in order to study the interactions between brain areas and neural dynamics [22]. Studies

suggest that synchrony communication between frontal and parietal regions support working memory processes [23].

Our electrophysiological variable of interest is the Gamma band (30 and 80 Hz) [24-27] because of its strong relationship with cognitive processes [28], such as attention, working memory and sensorimotor integration [29-31]. Previous studies reported a decrease in gamma coherence (GC) as an electrophysiological marker of cognitive impairment [24,31]. At the same time, several laboratories have reported an increase in amplitude of gamma-spectrum during sensory and cognitive processes [28,33-35]. GC has been used in psychiatric studies, investigating bipolar disorder [27,32], schizophrenia [24] and autism [36]. Until the present moment, there is none published study correlating PD and GC, what could be relevant to describe the interference of anxiety on communication of brain areas and how this can affect the information processing. A large portion of computer simulation (CS) potential regarding the research of PD and GC is still unexplored [15].With this in mind, we investigated whether PDP manifest working memory impairment and how an anxiogenic CS movie can interfere in a visual oddball task performance.

We hypothesized that the patients diagnosed with PD will present a disturbance in frontoparietal communication, expressed by lower gamma coherence when compared with HC. This hypothesis is based on the already documented working memory impairment in anxiety disorders [40, 41] and PD [39]; and the relationship between gamma coherence and working memory [40-42]. Therefore, the aims of the present study are: 1) to analyze if there is a difference between PDP and HC in gamma coherence of frontoparietal network; 2) to verify if the high levels of anxiety (produced by a computer simulation) affect working memory of PDP.

Material and Methods:

Sample

The sample was composed of 10 healthy, right-handed controls (1 male and 9 female with average age of 38.2, SD: 13.69), and 9 Panic Disorder Patients (9 female with average age of 48.8, SD: 11.16), 8 right-handed and 1 left-handed, with ages varying between 20 and 60 years old. The groups were matched by age. A t-Test-t was performed between the two groups and showed that there was no significant difference between these two groups ($p \geq 0.05$).The subjects were recruited from the Psychiatry

Institute of the Federal University of Rio de Janeiro. These participants were under psychiatric treatment or post cognitive behavioral therapy treatment. Thus, the psychiatrists and psychologists of our research team assessed them using the Mini International Neuropsychiatric Interview (5.0) and SCID-II. Inclusion criteria for patients required a current diagnostic of PD according to the DSM-V (Diagnostic and Statistical Manual of Psychiatric Disorders-fifth edition) [5]. Patients with comorbidities were excluded from the study. To avoid the pharmacological bias, they were asked to suspend medication one day before the exam. Seven patients were under pharmacological treatment and suspended the medication. All participants had normal or corrected-to normal vision and no sensory, motor, cognitive or attentional deficits. Participants who proved to have no present or past psychiatric condition and to be medically healthy upon physical examination were considered for the control group. All patients provided written informed consent before entering the study, according to the Declaration of Helsinki. The experiment was approved by the Ethics Committee of the Psychiatric Institute of the Federal University of Rio de Janeiro (IPUB/UFRJ).

Visual Oddball task

The oddball task is a useful method to evaluate information processing, event-related potential and reaction time [43,44]. The Visual Oddball paradigm consists of two stimuli presented randomly, with one of them occurring relatively infrequently. The stimuli randomization of the visual oddball task has as main objective to avoid any practical effect related to the learning of the task. The subjects need to discriminate target (infrequent) from non-target or standard stimuli (frequent). In the present experiment, target stimuli were represented by a square and non-target stimuli by a circle. Subjects were instructed to respond as quickly as possible to the target stimulus by pressing a button on a joystick (Model Quick Shot- Crystal CS4281). Each stimulus lasted 2.5 seconds, being the same interval time between stimuli, with the screen turned off. The baseline was defined as the mean voltage over 120 ms before the onset of the stimulus. Each subject was submitted to eight blocks of 20 trials. In other words, the square was presented 20 times in each moment, and 160 times to each subject.

Computer simulation

The simulation was used in previous research studies that confirmed it as a useful method to induce anxiety [45-47]. It was a 4-minute three-dimensional computer

animation developed by TriptyqueLAB (www.triptyquelab.com). The 4 minute CS consisted of 30 seconds of white screen, followed by 3 minutes of anxiogenic situations, and then more 30 seconds of white screen. The animation was in a first person perspective and starts at a bus stop, the bus arrives, the subject gets in and sits on the bus, the bus moves through city streets, stops again, is filled with people, moves through the streets, gets in a tunnel, stops inside the tunnel because of the traffic, starts moving again, leaves the tunnel, stops at a bus stop, the subject gets out of the bus and watches the bus drive away [45-47]. The simulation included sounds related to the images context. The subjects were exposed to the computer simulation just once.

Experimental Procedures

The EEG recordings (i.e., rest, stimulus presentation and CS) were conducted in an electrically shielded and sound and light-attenuated room. Individuals seated in front of a 15'' monitor, on a comfortable chair to minimize muscular artifacts. EEG data were collected before, during and after the tasks. The subjects were asked to rest for three minutes with the eyes open. After this, the participants executed the visual oddball task 1 and more three minutes of EEG record at rest. Then we presented the CS and after this, the participants were asked to rest three minutes with the eyes open, performed the visual oddball task 2 and three more minutes at rest. The objective was to observe how anxiety affects the information processing and working memory of PDP. The visual stimulus was presented on the monitor by the Event-Related Potential (ERP) Data Acquisition Software (Brain Mapping and Sensorimotor Integration Laboratory, Rio de Janeiro, Brazil), developed in Delphi 5.0 (Inprise Co.). The experiment was conducted in the Electrophysiology and Neuropsychology of Attention Laboratory (figure 1).

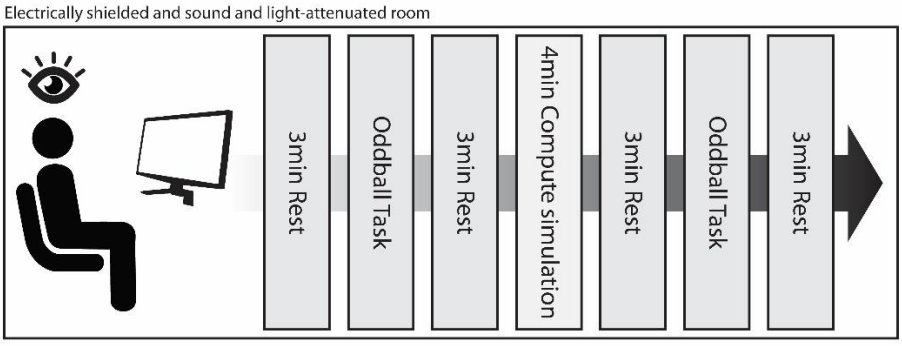

Figure 1: Experimental design

Data acquisition

Electroencephalography – EEG recordings were done using the 20-channel BrainNet BNT36 (EMSA Medical Equipment, Rio de Janeiro, Brazil). Electrode impedances were kept below 5 kΩ for the continuous EEG recording, data was sampled at 200Hz. The software ERP Data Acquisition was employed to filter the raw data: notch (60 Hz), high-pass of 0.1 Hz and low-pass of 100 Hz. During the presentation of ERP Data Acquisition and the CS, EEG activity was recorded from 20Ag/AgCl electrodes (SpiderCap, Brain Mapping and Sensorimotor Integration Laboratory, Rio de Janeiro, Brazil), placed in accordance with the extended version of the International 10/20 System, with earlobes electrodes as online reference, and an electrode attached beneath the right eye for recording the electrooculogram (EOG) and quantification of ocular artifacts. Visual artifacts were a priori inspected through a data visualization program using the Matlab 5.3® (The Mathworks, Inc.).

Data processing

The offline-preprocessing was performed using the EEGLAB software (freely available from http://sccn.ucsd.edu/eeglab) and included the following steps. To correct for ocular and muscular artifact (i.e., blink, muscle contraction), the visual inspection and Independent Component Analysis (ICA) were used. ICA is an information maximization algorithm that derives spatial filters by blind source separation of the EEG signals into temporally independent and spatially fixed components [48,49]. The data were collected using the bi-auricular reference and they were re-referenced using the average reference after artifact elimination. Afterwards, stimulus locked epochs were computed comprising an interval of -0,5s to + 1,5s corresponding to stimulus presentation. Trials were then baseline-corrected. Data from single-trial epochs exhibiting excessive movement artifact (± 70 μV) were also deleted. To correct for residual artifacts, a visual inspection procedure was used based on the epoch data. Thereby 8.3 epochs were rejected on average per visual oddball task. Incorrect responses were discarded.

Then, a classic estimator was applied for the power spectral density (PSD), or directly from the square modulus of the FT (Fourier Transform), which was performed by MATLAB (Matworks, Inc.). The electrophysiological measure was analyzed by coherence. It represents a measurement of linear covariation between two signals in the frequency domain. It is mathematically bounded between zero and one, whereby one

signifies a perfect linear association and zero denotes that the signals are not linearly related at that particular frequency. The premise is that when activities from spatially remote events simultaneously vary they tend to interact, also denoted as functional connectivity. Standard coherence as a measure of functional coupling provides a link between two signals but no directional information [33,50].

Statistical analysis

The statistical design allowed the examination of functional communication between the frontal and parietal areas in each hemisphere. All results are given as mean values and error deviation. We performed a two-way ANOVA (2x4) to analyze the factors: Group (Panic Disorder Patient or Healthy Control) and the Moments (Moment 1: 0,5s pre-stimulus visual oddball 1; Moment 2: 0,5s post-stimulus visual oddball 1; Moment 3: 0,5s pre-stimulus visual oddball 2 stimulus; Moment 4: 0,5s post-stimulus visual oddball 2) for each pair of electrodes separately: F7-F3, Fp1-F3, F3-Fz, F3-P3, F7-P3, P3-Pz, F4-F8, Fp2-F4, Fz-F4, F4-P4, F8-P4, Pz-P4 and Fp1-Fp2. Moreover, we used the Scheffé correction to address the problem of multiple comparisons.

In order to analyze the reaction time statistic, after found the mean values and error deviation, we performed a two-way ANOVA (2x2) for the factors Group (Panic Disorder Patients or Healthy Controls) and Moments (visual oddball 1 and visual oddball 2). The outcome of statistical calculations was declared significant if $p<0.05$. For statistical analysis we used SPSS package (version 22.0).

In order to determine the degree of synchronization between the activations of the pair of electrodes analyzed, we performed the event related cross-coherence using the EEGLAB (Matworks, Inc.).

Results:

Electrophysiological Results – Gamma Coherence

We divided the Electrophysiological Results according to the hemisphere localization.

Left hemisphere

We did not find interaction effect between the factors Group and Moments for the pairs of electrodes over the left hemisphere. Meanwhile, we found a main effect for Moment for **F3-P3** pair of electrodes (p=0.001; F=5.395). The Post-Hoc Scheffé showed that the moment 4 differs from the moment 1 and from the moment 2. Specifically, we observed a lower gamma coherence for the moment 1 and the moment 2 when compared to the moment 4 (p=0.003 and p=0.038 respectively) (figure 2).

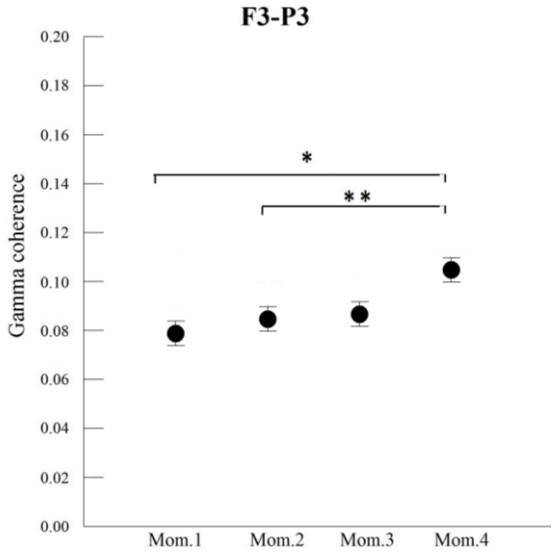

Figure 2: F3-P3 pair of electrodes: Mean and error deviation (ED) of gamma coherence for main effect of Moments (p=0.001).

The statistical analysis (figure 3) demonstrated a main effect of group for P3-Pz and F7-F3 pairs of electrodes. The PDP showed a smaller gamma coherence when compared to the HC for the P3-Pz pair of electrodes (p=0.003; f=8.854). The PDP showed a higher gamma coherence when compared to the HC group for the F7-F3 pair of electrodes (p=0.005; F=8.170).

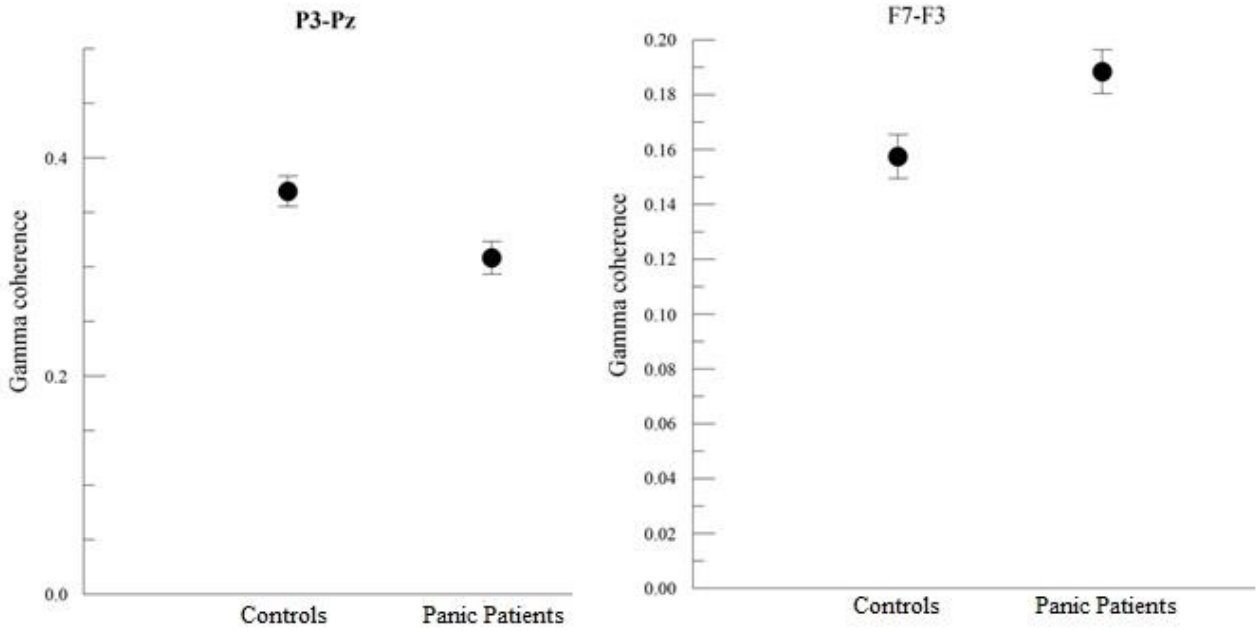

Figure 3: The mean and ED of gamma coherence for main effect of group for: (a) P3-Pz (p=0.003); (b) F7-F3 (p=0.005) pairs of electrodes.

Right hemisphere

We also did not find interaction effect between the factors Group and Moment for the pairs of electrodes over the right hemisphere. However, we observed a main effect of Group for **F4-F8** (p=0.028; f=4.882), **Fp2-F4** (p=.000; f=17.422) and **F4-P4** (p=0.013; f=6.319) pairs of electrodes. We identified greater gamma coherence for the HC when compared to PDP for the F4-F8 and Fp2-F4 pairs of electrodes (figure 4). Moreover, we found higher gamma coherence for PDP when compared to HC for the F4-P4 pair of electrodes (figure 5).

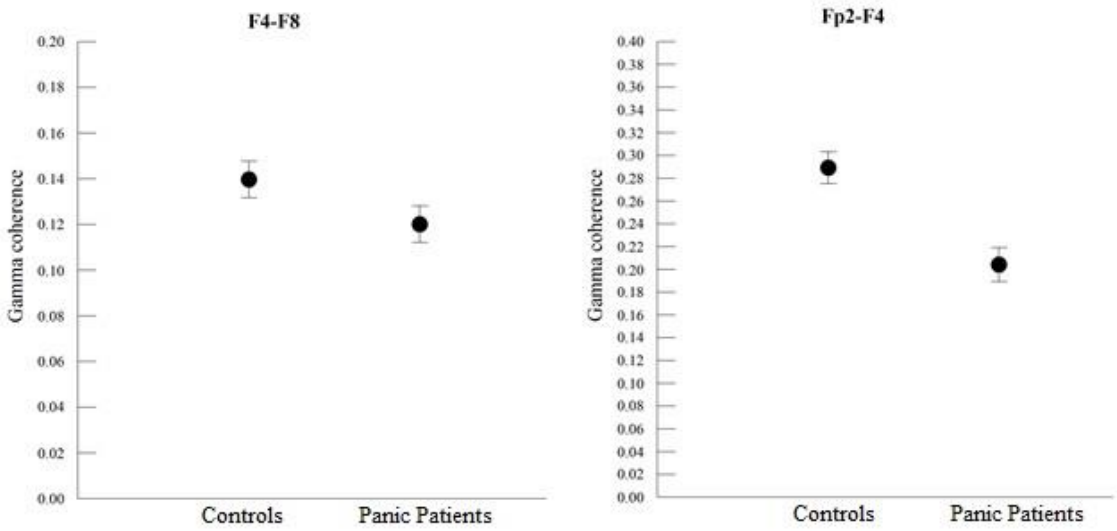

Figure 4: Mean and ED of gamma coherence for main effect of Group for: (a) F4-F8 (p=0.028); (b) Fp2-F4 (p=.000) pairs of electrodes.

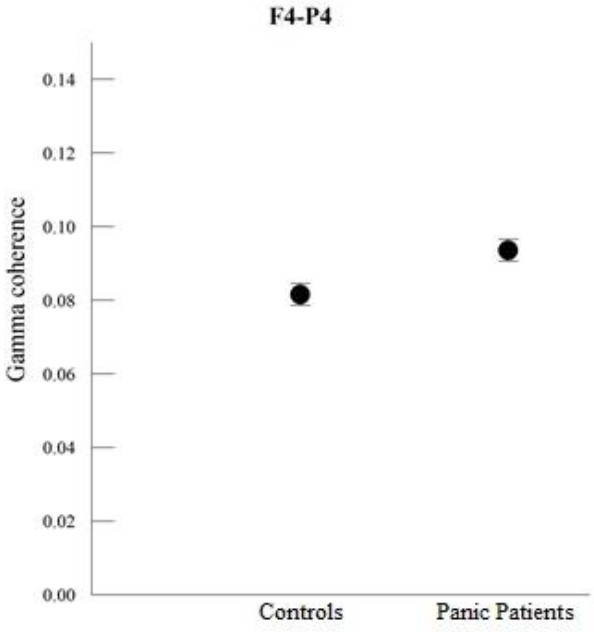

Figure 5: F4-P4 pair of electrodes: mean and ED of gamma coherence for main effect of group (p=0.013).

Behavioral Result – Reaction Time (RT)

We found a main effect for Group ($p<0.05$), but not for moment. We observed that HC (average: 488.06 ms, ED: 40.67 ms) was slower than PDP (average: 437.01 ms, ED: 37.55 ms). It is important to say that the CS did not significantly affect the RT performance after the movie. Both PDP and HC presented a faster RT in the oddball task 2 (figure 6).

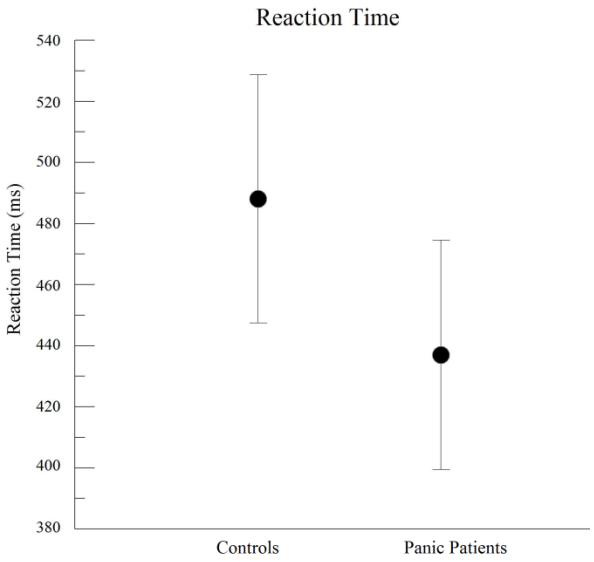

Figure 6: Mean and error deviation of reaction time for main effect of group ($p<0.05$).

Event-related cross-coherence

We found significant difference between the pairs of electrodes Fp2-F4, F4-F8 and F4-P4 for the event-related cross-coherence analysis. The plot highlighted the difference of gamma coherence between the groups during the 0,5s pre-stimulus and 0,5s post-stimulus.

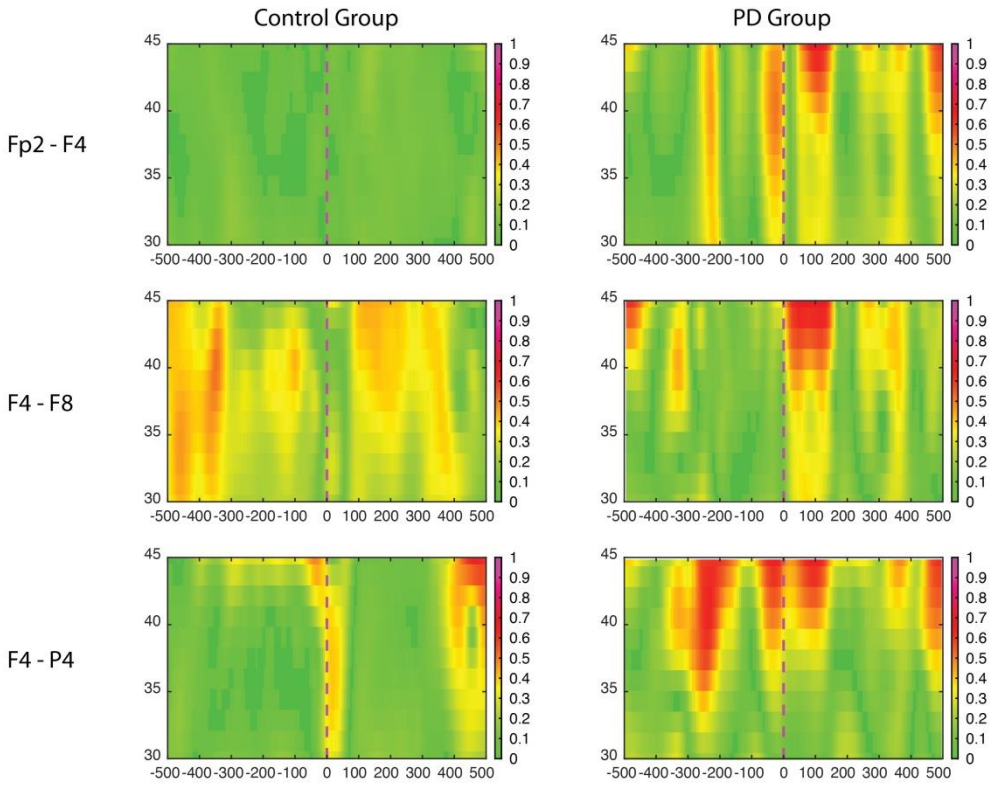

Figure 7: Event-related cross-coherence between the pairs of electrodes: Fp2-F4; F4-F8; F4-P4 for each group – HC and PDP. Bootstrap significance level to 0.05.

Discussion:

This present study is the first one to investigate the role of frontoparietal gamma coherence in PDP *versus* HC while the participants performed a working memory task, represented by the oddball paradigm. We also examined the influences of anxiogenic situations, produced by a CS, over the frontoparietal gamma coherence and the working memory. We hypothesized that the patients diagnosed with PD would present a disturbance in frontoparietal communication, expressed by lower gamma coherence when compared with HC.

Our main result indicated that the left frontoparietal network is the only area affected by the CS, with a gamma coherence increase during moments 3 and 4 (figure 2); demonstrating a left frontoparietal participation in the processing of anxiogenic stimuli. Although we did not find differences between the two groups investigated, we assumed that the movie exposed the participants to ordinary anxiogenic situations, for example crowded bus entering a tunnel, giving passengers a sense of unease. Different models of brain asymmetry are proposed for emotional processing [51-53]. The results of gamma coherence of F3-P3 (figure 3) and F4-P4 (figure 5) pairs of electrodes highlighted the difference between these brain networks during the anxiety processing and the interference of a working memory task.

The left brain hemisphere is associated with emotional processing [51,52] and we assumed that anxiety or negative emotions affected the gamma connectivity in this region. Goldstein [51] showed that damage to the left hemisphere was more likely to cause a catastrophic-depressive reaction in psychiatric patients than damage to the right hemisphere. Gupta and Pandey [54] revealed that depression and some forms of anxiety (trait and free-floating anxiety) were associated with enhanced right hemispheric performance on emotion processing tasks but not on tasks requiring processing of non-emotional information. If anxiety affects the gamma coherence in the left hemisphere, could panic symptoms be related to this impaired connectivity? Future studies about brain asymmetry should explore if PDP present a permanent or temporary (in the presence of anxiety) condition that impairs emotional processing. The valence hypothesis model [52] proposed that the pattern of hemispheric dominance depends on the emotional valence of the stimulus. The model proposes the left hemisphere is dominant for processing positive emotions, and the right hemisphere is dominant for

processing negative emotions. Contrary to Davidson's [52] model, our results pointed that anxiety and negative emotions interfere in the left hemisphere gamma connectivity, mainly over the frontoparietal network.

On the other hand, gamma coherence in the right frontoparietal network is activated by cognitive tasks, including visual oddball [55], inhibitory [56] and working memory tasks [57], and this network has been related to cognitive control. The right hemisphere also has an important role in emotional components processing [52,58], being important for processing primary emotions, such as fear [59]. The two hemispheres have a complementary specialization for control of different aspects of emotion [60]. It can be seen in the amygdala, since the right amygdala plays a role in the nonconscious processing of emotion, while the left amygdala is involved in the processing of conscious emotions [61]. Fassbender et al. [62] suggested that right frontoparietal cortex may be involved in allocating top-down attentional resources in a variety of cognitive tasks and may explain why this network of anatomical regions is consistently seen to be active during many different cognitive paradigms. The activation of frontoparietal regions for both cues and inhibitions reflects a common underlying control or attentional process [62]. As the anxiogenic movie didn't affected gamma coherence in the right frontoparietal network during the oddball task, based on this specific result, we cannot confirm that anxiety interferes in working memory. However it will be better discussed next, since we found a significant difference between the groups.

We did not find difference in the F4-P4 pair of electrodes (figure 5) for the moments, so we can suppose that there is a hemispheric difference between these networks in the processing of anxiety that can interfere in performance during a working memory task. In this way, the brain communication on the left hemisphere was affected by the CS movie. In other words, the anxiogenic stimuli caused some impairment on the communication of left brain regions that did not appear on the same areas of right hemisphere (F4-P4).

All the subjects performed the visual oddball paradigm, an experimental design that involves decision-making and working memory. In particular, working memory has been related with gamma coherence [40,41]. Therefore, we hypothesized that the PDP would present a disturbance in frontoparietal communication, expressed by lower gamma coherence when compared with HC, related to the execution of the experimental task. We did not corroborate our hypothesis in the frontoparietal communication;

however, we found the expected results for three pairs of electrodes located in the frontal and parietal areas, i.e., P3-Pz, F4-F8 and Fp2-F4 (figures 3 and 4). In other words, we observed greater gamma coherence in HC when compared to PDP, and the involvement of these areas was the expected results (figure 7).

The manual published by Trans Cranial Technologies [63] is an important reference about cortical functions. According to this the manual, these electrode areas are involved in different executive functions (e.g., executive control of behavior, inductive reasoning and planning), working memory (motor, visual, auditory, emotional, verbal), visuospatial processing, processing emotions and self-reflections during decision making, goal-intensive processing, episodic memory, declarative memory encoding, word and face encoding and modulating emotional response. When we observe the results of our gamma coherence study and remember the symptomatology of PD, we realize that PDP can present impairments on some of these functions. In this way, we decided that the low gamma coherence of PDP in these brain areas can contribute to a damaged brain communication in PD. This is reflected by the PDP's poorer performance in the execution of the visual oddball task, the impaired processing and modulation of stimuli related to anxiety of bodily sensations [6] – in a catastrophic way, – and the damage in working memory [12].

The results from these pairs of electrodes demonstrated an alteration of gamma coherence in PDP in these areas, supposing that PDP can present some interaction damage. Future investigations show that PDP can manifest difficulties in spatiality, multi-sensory integration, integration of information of environment, and others.

Contrary to our initial hypothesis, we found greater gamma coherence of PDP in F7-F3 and F4-P4 pairs of electrodes (figures 3 and 5). We can gather from this result that enlarged gamma coherence produces a prejudicial "noise" during information processing, and can be associated with an interference in the communication between the brain areas, and consequently in the information processing [32, 44]. The received information is processed and sent to the frontal areas for a decision making to be done. This interference between the areas of communication could be related to the abnormal processing of PDP.

With results of higher communication in the frontal region that is typically responsible for language, thought and self-talking (that is very common in anxiety), can lead us to the following questions: can the greater gamma coherence of PDP be related to accelerated thoughts and other symptoms of PD and anxiety disorders, and is this

greater gamma coherence associated with an impairment of information processing. Velasques et al. [32] found higher gamma coherence in bipolar patients during the manic state. According to these authors, the high gamma coherence expresses a higher coupling between electrode sites. This produces a more intense binding between areas, with more sensory information exchange, that interferes and provokes acceleration in information processing.

A systematic review conducted by Di Giorgio et al. [65] demonstrated that many researchers of PD note that PDP present impairment in information processing. This can be related to a non-specific dysfunction in the limbic-reticular structures that affect active, focused and short-term attention, working and short-term memory and recognition and decision making. These data highlight an inability in PDP's to automatic cognitive processes to respond to new stimuli. PDP exhibit excessive reactivity in environments with high sensitive load such as bodily sensations or crowded places.

This impairment can be associated with the symptomatology of PD that is characterized by an inadequate interpretation of internal (bodily sensations) and external (environmental) stimuli as dangerous and catastrophic, which could be related to a failure to automatically inhibit responses to fear or failure in the modulation of more sophisticated and conscious responses.

The behavioral analysis of reaction time (RT) showed that PDP were faster than HC in the visual oddball task (figure 6). This raising the question: this can be the same faster reactivity to stimuli demonstrated by PDP, for example when they are in a crowd place. The research conducted by Pauli et al. [66] examined the limits of the perception of PDP. In this study, participants were asked to recognize anxiety related words next to neutral words. PDP had a significantly faster RT compared to HC when completing the same task. According to these authors, this finding indicates an explicit memory bias of PDP for anxiety related stimuli.

Anxiety can interfere with RT and caused a loss of accuracy. Castillo et al. [39] noted that high levels of anxiety in patients with PD could affect cognitive functioning. According to Dratcu and Bond [12], excitement and anxiety could lead to a loss of selective attention, which mediates the process of encoding information and support received. Therefore, these patients have a faster reactivity that is not accompanied by accuracy of the information processing. This could be explained by the fact that impulsivity is higher in patients with anxiety disorders than in HC [67]. Two studies

[39,68] found differences between PDP and HC in executive function, such as decision-making, inhibition of automatic responses, flexibility, and categorization.

Conclusion:

Our data revealed that there may be an optimal level of gamma coherence to obtain an appropriate brain functioning during attention tasks. An increase or decrease in gamma coherence could be associated with communication impairment between regions. Our results highlight an optimum level of coherence between areas to the healthy information processing. The observed lower or higher gamma coherence in some pairs of electrodes of PDP can be associated with a cognitive dysfunction of information processing in PD. The brain communication of the left hemisphere was affected by the anxiogenic stimuli, causing some impairment of the communication of left brain regions, which did not appear on the same areas of the right hemisphere. The small sample was a limitation of this study. There is still much to be researched in the area of electrophysiology about anxiety disorders. Therefore, we suggest the execution of more studies using the same methodology of gamma coherence with PDP, not only to observe the neurobiological differences between PDP and HC, but also the difference between the results that were found before and after the treatments with cognitive behavioral therapy and/or medicament treatment.

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4.3. Artigo III: **A virtual reality and electrophysiological investigation in panic disorder patients during the *oddball* paradigm.**

A virtual reality and electrophysiological investigation in panic disorder patients during the *oddball* paradigm.

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Abstract:

Panic disorder (PD) is an anxiety disorder characterized by repeated and unexpected attacks of intense anxiety, which are not restricted to a determined situation or circumstance. Researchers have been using the quantitative electroencephalography (qEEG) to examine topological changes in the connection of cognitive regions. We chose the alpha band (8–13 Hz) as our electrophysiological variable because of its relationship with the top down and inhibitory processes. The objective of this study is to analyze if there is a difference in frontoparietal absolute alpha power between panic patients and healthy controls (HC) during the *oddball* paradigm; and verify if high levels of anxiety (produced by a virtual reality movie) affect PD patients' working memory. Nine PP (9 female with average age of 48.8, SD: 11.16) and ten HC (1 male and 9 female with average age of 38.2, SD: 13.69) were enrolled in this study. The subjects performed the *oddball* paradigm

simultaneously to the EEG record before and after the presentation of virtual reality simulation. A two-way ANOVA was applied to analyze the factors Group and the Moment for each electrode separately, and another one to analyze the reaction time variable. We verified a decrease of alpha power of PD patients during the increased information processing associated with the task execution. We also observed a significant difference between the four moments, since the absolute alpha-power was growing over the advance of the moments. The behavioral analysis of reaction time (RT) demonstrated that PD patients were faster than HC in the *oddball* task, what may be related to the faster reactivity and high excitability to stimuli and symptoms related to PD. Our results are related to different PD symptoms, which should be better known and considered, in order to develop effective clinical treatment strategies.

Key words: Panic disorder – EEG – Absolute Alpha Power - Information Processing – working memory.

Introduction:

The neurobiology researchers have been studying panic disorder (PD) in the last years, to investigate the relationship between electrophysiology and its behavioral and cognitive symptoms. PD is an anxiety disorder characterized by repeated and unexpected attacks of intense anxiety, which are not restricted to a determined situation or circumstance, and which can result in palpitations and tachycardia, breathlessness, asphyxia, fear of death, fear of losing control and going insane, dizziness, depersonalization, derealization, and others (APA, 2013). According to the cognitive model of PD, these patients present an inadequate and dysfunctional processing of external stimuli (Pauli *et al*., 1997) and bodily sensations (Clark, 1986). A dysfunctional misinterpretation of some environment or bodily stimuli occurs as signs of danger, setting off the sympathetic activation and consequent bodily sensations of anxiety. These symptoms are processed as confirmation of the danger potential of stimuli or situation, which can induce a new panic attack (Rangé & Borba, 2008). This cognitive processing model is coherent with the neurobiological hypothesis that attributes the PD anxiety to a dysfunctional interaction between the pre-frontal cortex and the limbic system (Windmann *et al*., 2002). According to Gorman *et al*. (2000), a disability in the

coordination of stimuli from the cortex and brainstem could engender an abnormal activation of the amygdala, with a behavioral, autonomic, and neuroendocrine stimulation. Amygdala activation may be a consequence of misinterpretation of sensory information and it allows the cascade of neural events that is experienced as a panic attack (de Carvalho *et al*., 2013)

This neuroanatomical activation differences observed in PD conducted to the questioning of whose are the cognitive deficits related to PD? The systematic review conducted by O'Sullivan & Newman (2014) indicated an absence of difficulties in PD participants relative to HC, but the authors pointed that there was some support for potential impairments in short term verbal and visual memory in people with PD compared to HC. At the same time, the research results about the working memory performance in PD patients are controversial, some of them showed no impairments (Boldrini *et al*., 2005; Deckersbach *et al*., 2011), while others point an impairment in this cognitive function (Dratcu and Bond, 1998). That can be related to difficulties in the information processing and, consequently, to the misinterpretation of bodily symptoms. Dratcu and Bond (1998) explained that deficits in working memory and explicit memory may be related to a high level of excitement and anxiety in patients during the task execution.

Nowadays, neuroscience researchers have been using the VR technique to observe neurobiological parameters during and after the virtual contact with phobic environments or situations. In this context, the anxiety related to stimuli observed on the video can trigger anxiety symptoms, like body sensations. This technique allows the investigation of induced anxiety with PD patients in an environment fully controllable by the investigator (Riva, 2005). VR has been also used as a useful tool of psychotherapy focused on anxiety disorders (de Tommaso *et al*., 2016), since agoraphobia until specific phobias, like the driving phobia, as a mechanism for exposure therapy (de Carvalho *et al*., 2008).

As the quantitative electroencephalography (qEEG) has been used to the functional network analysis to examine topological changes in the connection of cognitive regions (de Tommaso *et al*., 2016; Pavone *et al*., 2016; Vourvopoulos & Bermúdez i Badia, 2016) in real-time (Dan & Reiner, 2016), we aimed observe the VR effects on human brain cognitive functions with PD patients. Our electrophysiological variable of interest is the alpha band (8–13 Hz), the predominant brain rhythm in awake and relaxed states. We chose this band because of its relationship with the top down and

inhibitory processes (Klimesch *et al*., 2007). In this way, a decrease in absolute alpha-power is related to increased cortical excitation, such as cognitive processing (Klimesch *et al*., 2007; De Carvalho *et al*., 2013) and anxiety (Wiedemann *et al*., 1998; Gordeev, 2008; Wise *et al*., 2011). This trait deficit in alpha activity has been proposed as a risk factor for a number of psychiatric disorders including anxiety disorders and alcoholism (Propping *et al*., 1980).

Alpha absolute power has been used in psychiatric researches, investigating impairments on the cognitive processing over different anxiety disorders (Wiedemann *et al*., 1998; Metzger *et al*., 2004; De Carvalho *et al*., 2008; Gordeev, 2008). Until the present moment, there is none published study correlating PD, absolute alpha power and the *oddball* paradigm, what could be relevant to describe the interference of anxiety on communication of brain areas and how this can affect the information processing. Furthermore, a large portion of VR potential regarding the research of PD and AG is still unexplored (De Carvalho *et al*., 2008).

In this context, we hypothesized that the patients diagnosed with PD will presents lower frontoparietal activation during the *oddball* task when compared with HC, expressed by lower alpha absolute power, mostly after high levels of anxiety (produced by a virtual reality movie). This hypothesis is based on the decreased absolute alpha-power in anxiety already documented (Wiedemann *et al*., 1998; Gordeev, 2008; Wise *et al*., 2011; De Carvalho *et al*., 2013). Therefore, the aims of the present study are: 1) to observe alpha absolute power during the *oddball* task in the frontoparietal network in PD patients compared to HC; 2) to verify if the high levels of anxiety affect working memory of subjects with PD, observing the alpha absolute power activation in the moments before and after watching an anxiogenic computer simulation (Freire *et al*., 2010)

.

Methodology:

Sample

The sample was composed of 10 healthy controls (HC - 1 male and 9 female with average age of 38.2, SD: 13.69), all right-handed, and 9 PP (9 female with average age of 48.8, SD: 11.16), 8 right-handed and 1 left-handed, with ages varying between 20 and 60 years old. Inclusion criteria is for patients required a current diagnostic of PD

according to the DSM-V (Diagnostic and Statistical Manual of Psychiatric Disorders-fifth edition, 2013), and they were asked to suspend medication one day before the exam. Patients with comorbidities were excluded from the study. The subjects were recruited from the Psychiatry Institute of the Federal University of Rio de Janeiro. All participants had normal or corrected-to normal vision and no sensory, motor, cognitive or attentional deficits. Participants who proved to have no present or past psychiatric condition and to be medically healthy upon physical examination were considered for the control group. All patients provided written informed consent before entering the study, according to the Declaration of Helsinki. The experiment was approved by the Ethics Committee of the Psychiatric Institute of the Federal University of Rio de Janeiro (IPUB/UFRJ).

Oddball task

The *oddball* task is a useful method to evaluate information processing, event-related potential and reaction time (Atagun *et al*., 2013; Hermens *et al*., 2005; Schulze *et al*., 2008; Wise *et al*., 2009). The *oddball* paradigm consists of two stimuli presented randomly, with one of them occurring relatively infrequently. The subjects need to discriminate target (infrequent) from non-target or standard stimuli (frequent). In the present experiment, target stimuli were represented by a square and non-target stimuli by a circle. Subjects were instructed to respond as quickly as possible to the target stimulus by pressing a button on a joystick (Model Quick Shot- Crystal CS4281). Each stimulus lasted 2.5 seconds, being the same interval time between stimuli, with the screen turned off. We divided the *oddball* task in four moments of 20 stimuli each.

Computer simulation

The simulation was used in previous research studies that confirmed it as a useful method to induce anxiety (Freire *et al*., 2010; De Carvalho *et al*., 2013; De Carvalho *et al*., 2015). It was a 4-minute three-dimensional computer animation developed by TriptyqueLAB (www.triptyquelab.com). The animation was in a first person perspective and starts at a bus stop, the bus arrives, the subject gets in and sits on the bus, the bus moves through city streets, stops again, is filled with people, moves through the streets, gets in a tunnel, stops inside the tunnel because of the traffic, starts moving again, leaves the tunnel, stops at a bus stop, the subject gets out of the bus and

watches the bus drive away (Freire *et al*., 2010; De Carvalho *et al*., 2013; De Carvalho *et al*., 2015). The simulation included sounds related to the images context.

Task procedures

The subjects performed the task in a sound and light-attenuated room, in order to minimize sensory interference. Individuals seated in front of a 15'' monitor, on a comfortable chair to minimize muscular artifacts, while electroencephalography was collected. First, EEG data was collected at rest for each subject during three minutes. After this, the participants executed two moments of the visual *oddball* task and more three minutes of EEG record at rest). Then we presented the computer simulation and after the participant executed two more moments of the *oddball* paradigm and three more minutes at rest. The objective was to observe how anxiety affects the information processing and working memory of PP. It is important to point that were recorded six moments of three minutes at rest: before the presentation of any stimuli, between *oddball* tasks and the simulation, and after the last moment of *oddball* task. The visual stimulus was presented on the monitor by the event-related potential (ERP) acquisition software, developed in Delphi 5.0 (Inprise Co.). The baseline was defined as the mean voltage over 120 ms before the onset of the stimulus. Each subject was submitted to four moments of 10 trials. In other words, the square was presented 10 times in each moment.

Data acquisition

Electroencephalography – The International 10/20 System for electrodes was used with the 20-channel EEG system Braintech-3000 (EMSA-Medical Instruments, Brazil). The software Data Acquisition (Delphi 5.0), developed at the Brain Mapping and Sensorimotor Integration Laboratory was employed to filter the raw data: notch (60 Hz), high-pass of 0.1 Hz and low-pass of 100 Hz. Visual artifacts were a priori inspected through a data visualization program using the Matlab 5.3® (The Mathworks, Inc.).

Data processing

To quantify reference-free data, a visual inspection and independent component analysis (ICA) were applied to identify and remove any remaining artifacts, i.e., eye blinks and ocular movements produced by the task. Data from individual electrodes exhibiting loss of contact with the scalp or high impedances (>10 kΩ) were deleted and

data from single-trial epochs exhibiting excessive movement artifact (± 100 μV) were also deleted. Independent component analysis (ICA) was then applied to identify and remove any remaining artifacts after the initial visual inspection. ICA is an information maximization algorithm that derives spatial filters by blind source separation of the EEG signals into temporally independent and spatially fixed components. Independent components resembling eye-blink or muscle artifact were removed and the remaining components were then back-projected onto the scalp electrodes by multiplying the input data by the inverse matrix of the spatial filter coefficients derived from ICA using established procedures. The ICA-filtered data were then reinspected for residual artifacts using the same rejection criteria described above.

Statistical analysis

The statistical design allowed the examination of functional communication between the frontal, parietal and temporal areas in each hemisphere. All results are given as mean values and error deviation. We performed an ANOVA two-way to analyze the factors Group (two levels: patients *versus* controls) and the Moment (four levels: 1- moment just before *oddball* 1 task; 2- moment after *oddball* 1; 3- moment before *oddball* 2; 4- moment after *oddball* 2) for each electrode separately: Fp1, Fp2, F3, F4, F7, F7, F8, T3, T4, T5, T6, P3, P4, Pz, O1, O2 and Oz. Moreover, we used the Scheffe correction to address the problem of multiple comparisons. In order to analyze the reaction time statistic, we performed an ANOVA two-way for the factors Group (two levels: patients *versus* controls) and Moment (two levels: *oddball* 1 *versus oddball* 2). The outcome of statistical calculations were declared significant if $p<0.05$. For statistical analysis we used SPSS package (version 22.0).

Results:

Electrophysiological Results – Alpha Absolute Power:

We divided the Electrophysiological Results according to the regions frontal, parietal and temporal.

Frontal Area:

In the left frontal area, we found interaction between the factors Group and Moment for the electrodes Fp1 (p=0.003; F=4.75), F3 (p=0.04; F=2.766) and F7 (p=0.006; F=4.112). For the electrodes of the right hemisphere, the results pointed a main effect for Group and Moment for the electrodes Fp2 (group: p=0.00; F=86.360/ moment: p=0.00; F=13.054), F4 (group: p=0.003; F=8.594/ moment: p=0.002; F=4.785) and F8 (group: p=0.00; F=12.734/ moment: p=0.00; F=19.544). While in the midline electrode Fz we found interaction between the same factors (p=0.004; F=4.458).

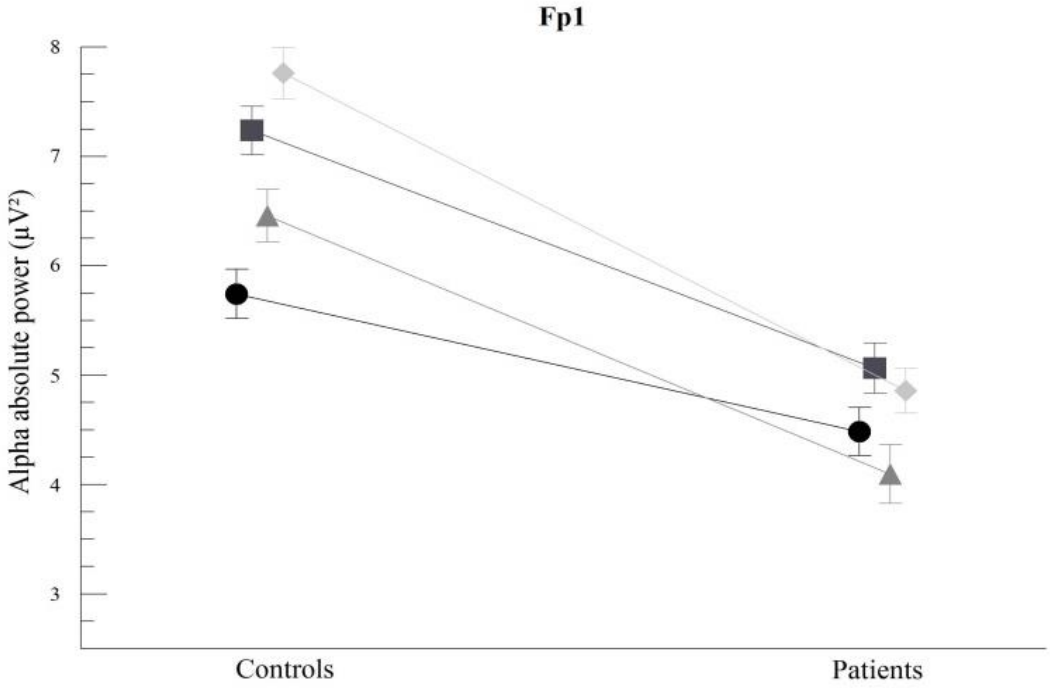

Figure 1: Mean and error deviation of absolute alpha power for Fp1 electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.003).

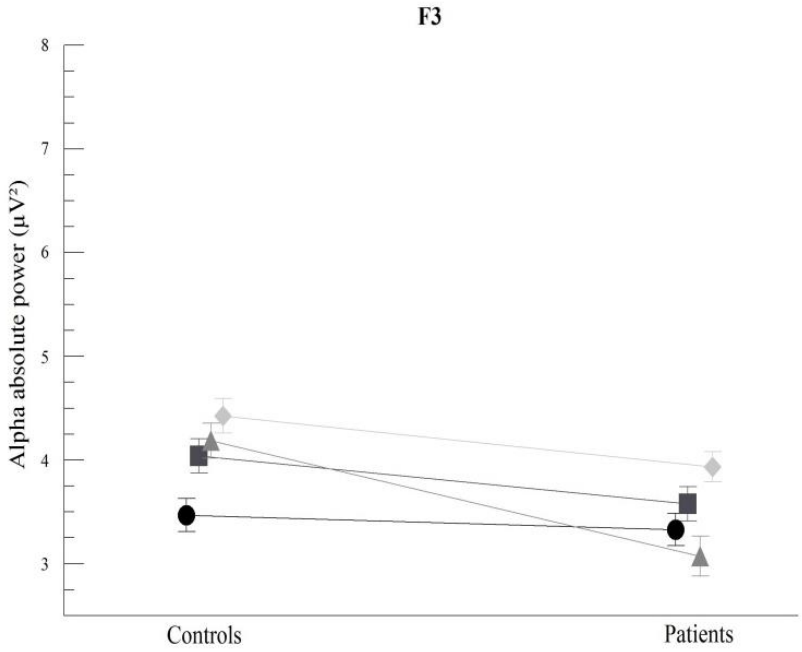

Figure 2: Mean and error deviation of absolute alpha power for F3 electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.04).

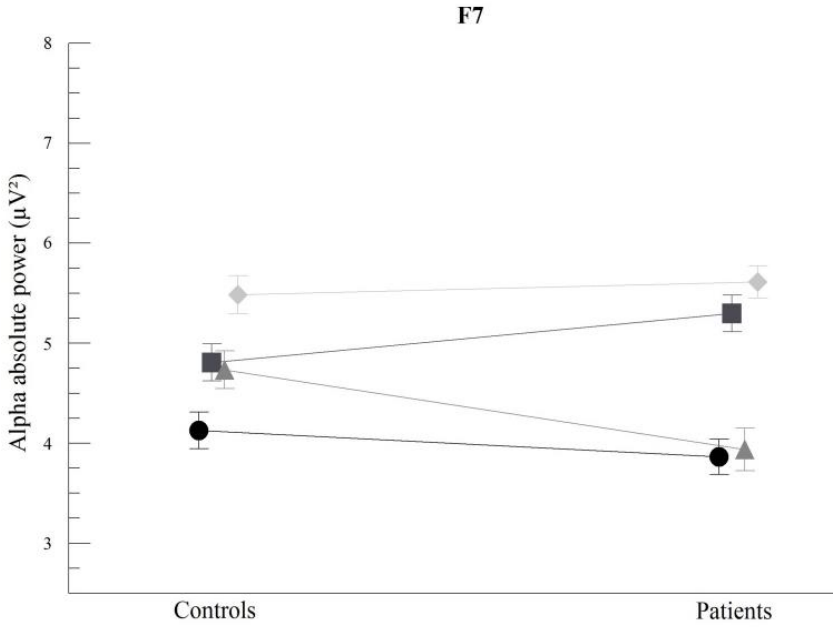

Figure 3: Mean and error deviation of absolute alpha power for F7 electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.006).

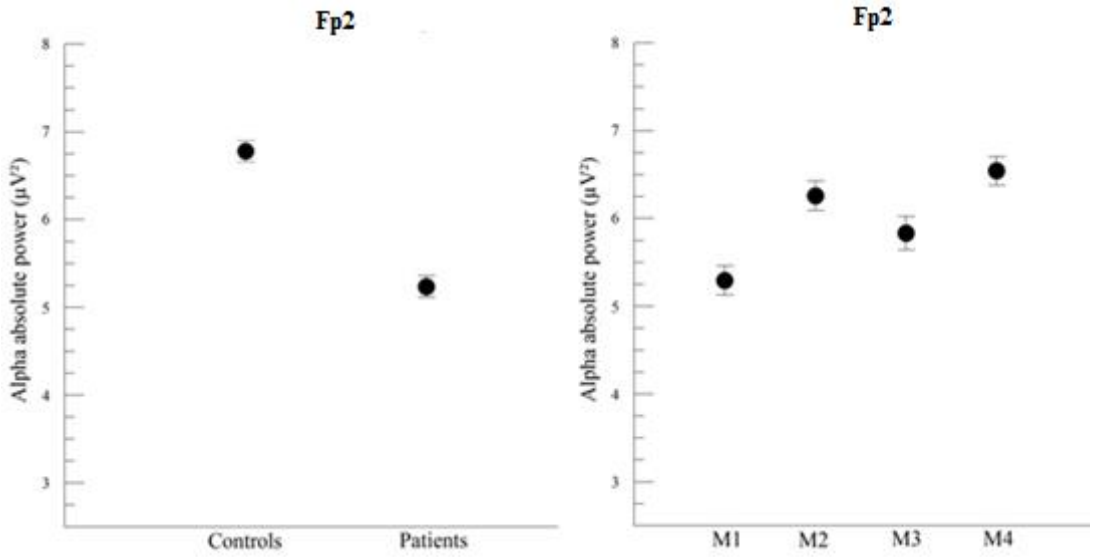

Figure 4: Mean and error deviation (ED) of alpha absolute power for Fp2 electrode. The bars represent ED. A 4x2 ANOVA designs showed a main effect of group (p=.000) and moment (p=.000) for Fp2.

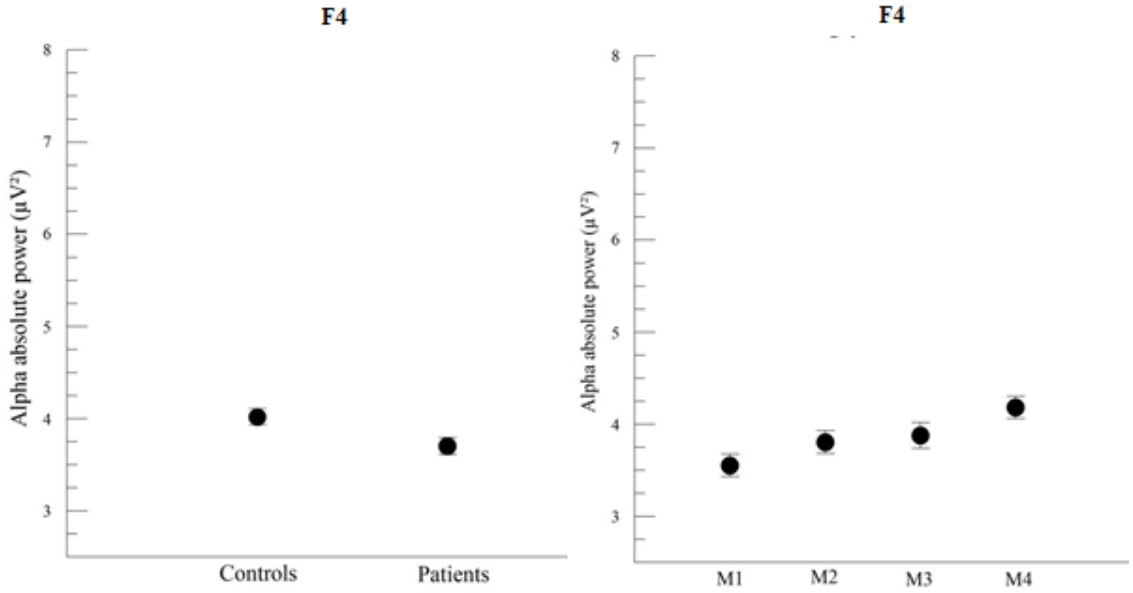

Figure 5: Mean and error deviation of alpha absolute power for F4 electrode. The bars represent ED. A 4x2 ANOVA designs showed a main effect of group (p=.003) and moment (p=.002) for Fp2.

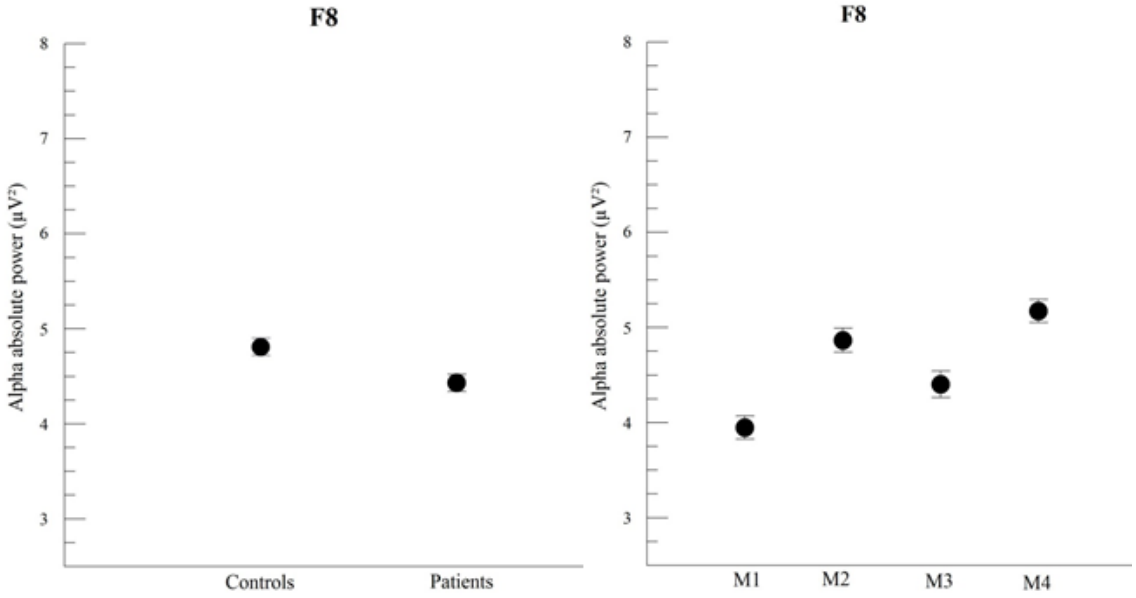

Figure 6: Mean and error deviation of alpha absolute power for F8 electrode. The bars represent E.D. A 4x2 ANOVA designs showed a main effect for group (p=0.00) and moment (p=0.00).

Meanwhile, we found in the parietal region over the P3 electrode a main effect for Moment (p=0.00; F=6.828) and Group (p=0.00; F=55.743). We observed the lowest absolute alpha-power for the moment preceding the *oddball* task pre-stimulus (moment 1), while the highest absolute alpha-power was the moment after the *oddball* task after-movie (moment 4). We found an interaction between the factors Group and Moment for the electrode P4 (p=0.00; F=7.711) and Pz (p=0.005; F=4.294).

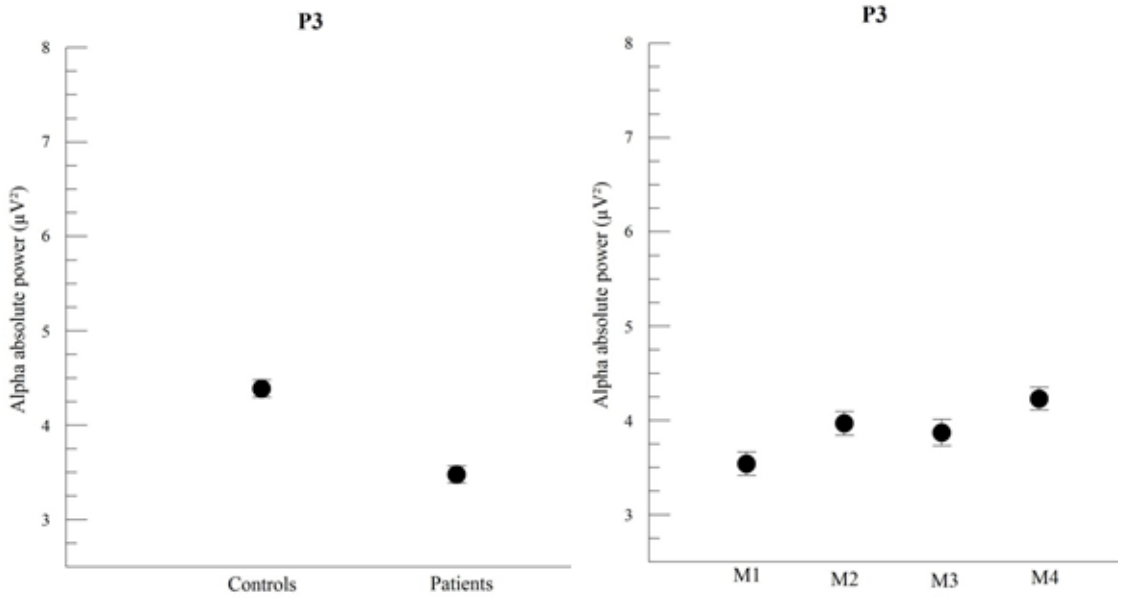

Figure 7: Mean and error deviation of alpha absolute power for P3 electrode. The bars represent E.D. A 4x2 ANOVA designs showed a main effect for group (p=0.00) and moment (p=0.00).

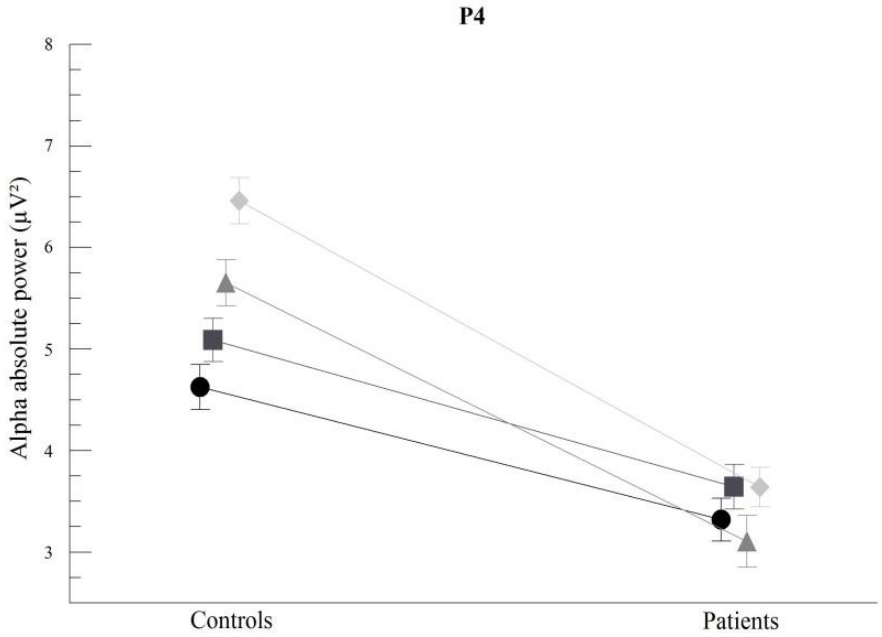

Figure 8: Mean and error deviation of absolute alpha power for P4 electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.00).

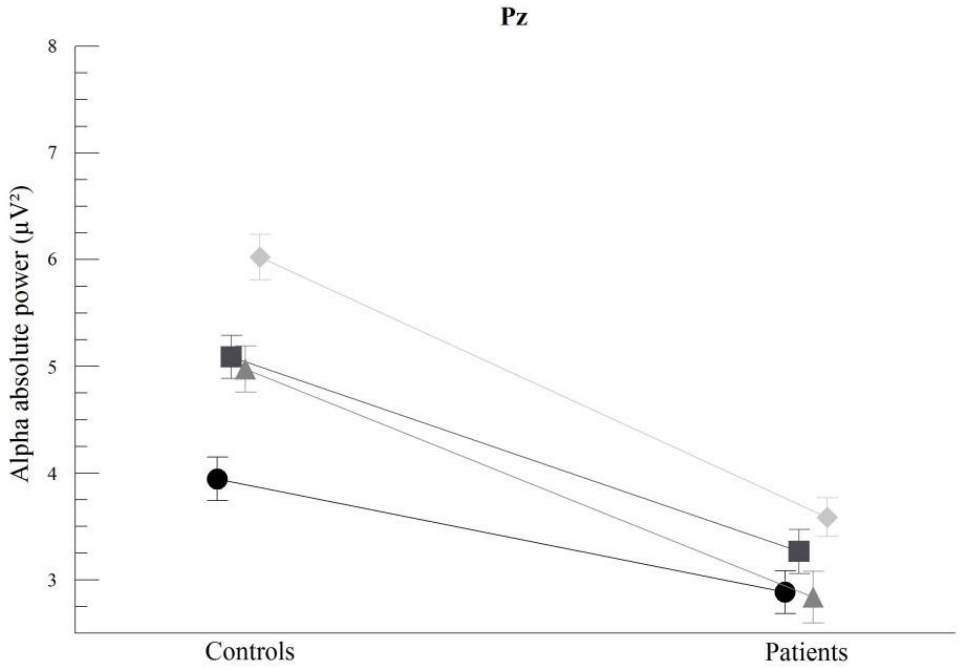

Figure 9: Mean and error deviation of absolute alpha power for Pz electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.005).

In the temporal area, we found interaction between the factors Group and Moment for the electrode T3 (p=0.00; F=6.273) and a main effect for Moment in the electrode T5 (p=0.001; F=5.666). Over the right hemisphere, we found an Interaction between the factors for T4 (p=0.00; F=7.711) and T6 (p=0.007; F=3.996).

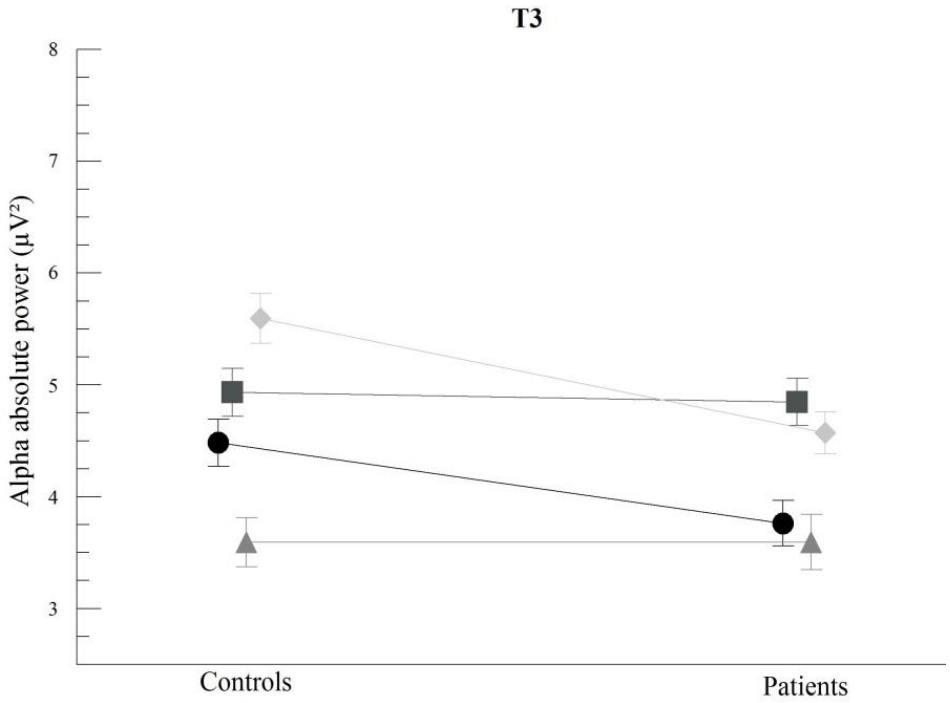

Figure 10: Mean and error deviation of absolute alpha power for T3 electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.00).

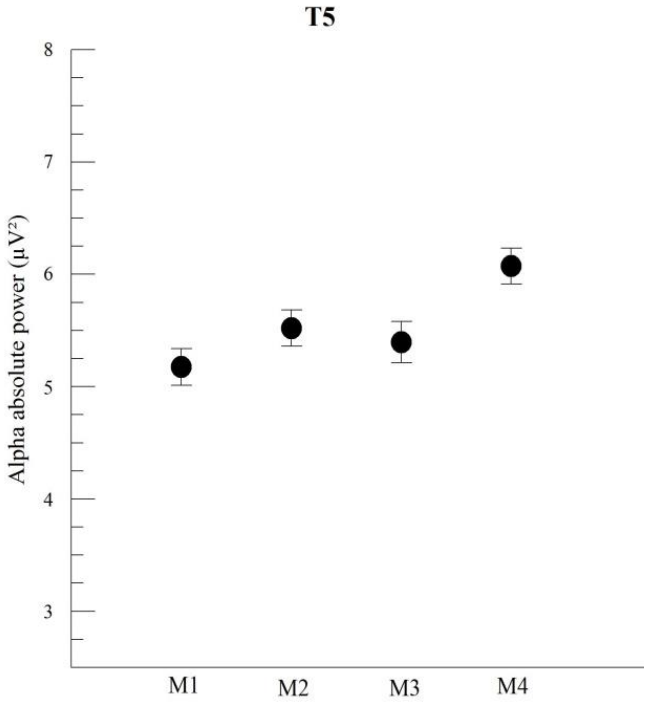

Figure 11: Mean and error deviation of alpha absolute power for P3 electrode. The bars represent E.D. A 4x2 ANOVA designs showed a main effect for moment (p=0.001).

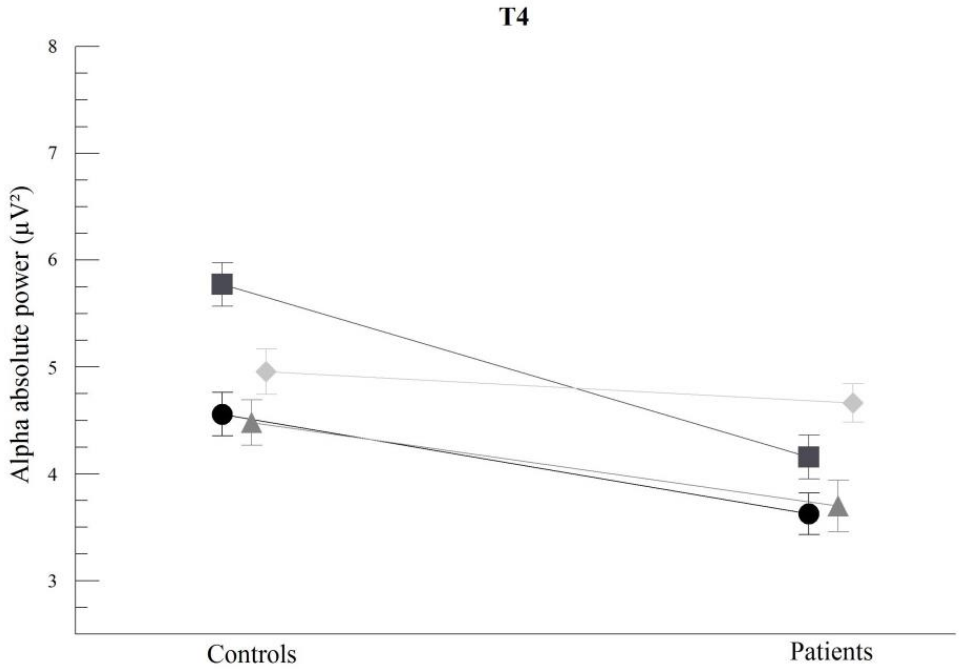

Figure 12: Mean and error deviation of absolute alpha power for T4 electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.00).

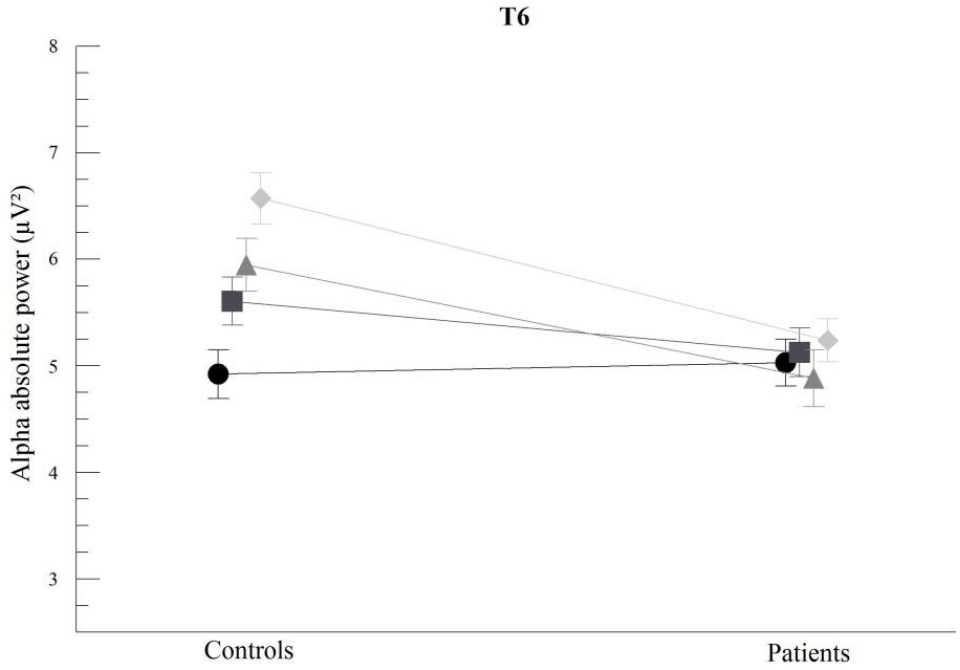

Figure 13: Mean and error deviation of absolute alpha power for T6 electrode. The bars represent E.D. A 4x2 ANOVA designs showed an interaction between the factors group and moment (p=0.007).

The results of interaction between the factors Group and Moment for the electrodes Fp1, F3, P4, Pz, T3, T4 and T6 showed that under the study conditions the PD patients presented a decrease of absolute alpha-power when compared to HC. The F7 and Fz electrodes results demonstrated exceptions. In all the electrodes Fp2, F4, F8, P3 and T5, where we found a main effect for Moment, both groups demonstrated a lowest absolute alpha-power in the moment 1 and highest in the moment 4. In the electrodes that we found a main effect for group, that were Fp2, F4, F8 and P3, the absolute alpha-power was lower for PD patients than for HC.

Behavioral Result – Reaction Time (RT)

We found a main effect for Group ($p<0.05$), but not for moment. We observed that HC (average: 488.06 ms, ED: 40.67 ms) was slower than PD patients (average: 437.01 ms, ED: 37.55 ms). It is important to say that the VR did not significantly affect the RT performance after the movie. Both PD patients and HC presented a faster RT in the second *oddball* task.

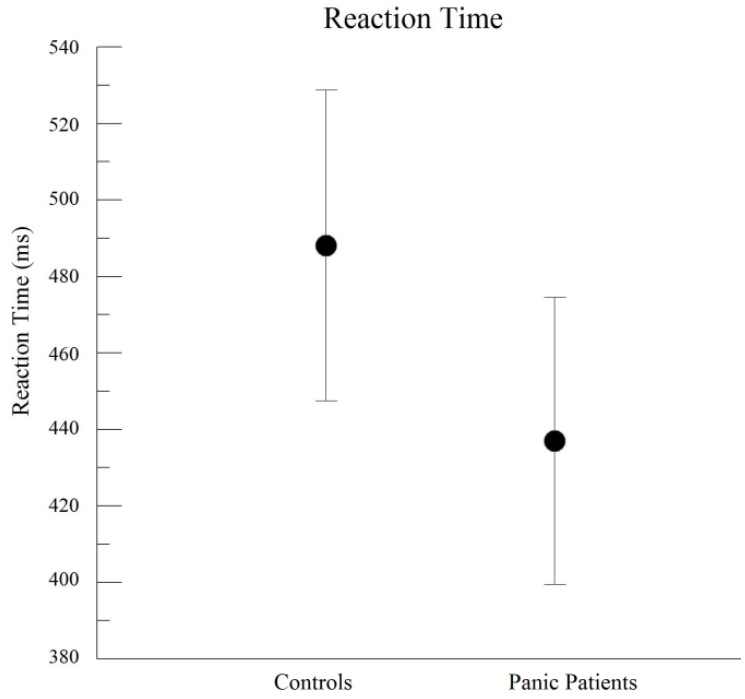

Figure 14: Mean and error deviation of reaction time. The bars represent E.D. A 2x2 ANOVA designs showed a main effect of group for reaction time ($p<0.05$).

Discussion:

This present study investigated the role of absolute alpha-power over the frontal, parietal and temporal areas in PD *versus* HC while the participants performed a working memory task, represented by the *oddball* paradigm. We also examined the influences of ansiogenic situations, produced by a virtual reality movie, over the absolute alpha-power and the working memory. In addition, we decided to analyze the 4 minutes movie, and we made no comparisons between the low and high anxiety scenes in this paper.

Our main result indicated that in the investigated areas the absolute alpha-power was decreased in PD patients that were submitted to an ansiogenic VR movie, during the execution of a working memory task. This result is according to previous studies that reported a low absolute alpha-power in PD patients (Siciliani *et al*., 1975; Enoch *et al*., 1995; Kalashnikova and Sorokina, 1995; Wiedemann *et al*., 1998; Gordeev, 2008; Wise *et al*., 2011, De Carvalho *et al*., 2013). In the study conducted by De Carvalho *et al*. (2013) a greater absolute alpha-power for healthy subjects were found when compared to the PD patients in the frontal area, what were interpreted as a greater frontal activation that could be related to an impaired frontal attempt to regulate downstream excitability or to the reflection of the excitation originated from deeper subcortical regions.

Klimesch *et al*. (2007) hypothesized that the decreased absolute alpha-power may reflect a dysfunction in thalamic–cortical circuits that is associated with incapacity to inhibit irrelevant information, role played especially by the PFC. This understanding can be related to the Beck *et al*. (1992) theory, which pointed that PD patients tend to be hypersensitive even for lower anxiety stimulus, exhibiting hyperousal responses, as they are hypervigilant to danger cues. So these patients can present a dysfunctional processing of external stimuli (Pauli *et al*., 1997) and bodily sensations (Clark, 1986). Besides that, this decreased alpha-power could affect the top-down functions, thus the PD patients may present impairment both in inhibitory control and top-down regulation during the anxiety state, what is related to the state of high excitability and lower inhibitory control (Gordeev, 2008; Pavlenko *et al*., 2009).

If the PFC top-down modulation is not working properly, anxiety symptoms are likely to be more prominent (De Carvalho *et al*., 2013). The low absolute alpha power for left prefrontal and left frontal region found is also in line with the possibility of an impaired top-down regulation and inhibition control. Two studies (Castillo *et al*., 2010; Airaksinen *et al*., 2005) found differences between PD patients and HC in executive

function, such as decision-making, inhibition of automatic responses, flexibility, and categorization.

While the decrease of absolute alpha-power represents a high excitability state, the higher alpha-power presented by the HC can be related to a low excitability state (Gordeev, 2008). This way, our result of greater alpha-power for HC when compared to PD patients may highlights a dysfunctional activation and regulation of excitability over the frontal, parietal and temporal networks of PD patients.

In a systematic review, Di Giorgio *et al*. (2013) evidenced that many PD researchers noted that PD patients present impairment in information processing. The inability in PD patients to automatic cognitive processes to respond to new stimuli in consequence of excessive reactivity in environments with high sensitive load, can be associated with the symptomatology of PD that is characterized by an inadequate interpretation of internal (bodily sensations) and external (environmental) stimuli as dangerous and catastrophic, which could be related to a failure to automatically inhibit responses to fear or failure in the modulation of more sophisticated and conscious responses (Di Giorgio *et al*., 2013).

Another important result of this research was the difference between the moments. In all the electrodes that presented a main effect for moment, the absolute alpha-power was growing over the advance of the moments, thus the moment 1 was smaller than the second moment and so on. We believe that it may be related to the fact that the absolute alpha power decreases during the anxiety state, so we can suppose that both groups were more anxious in the beginning of the task (moment 1), just before the presentation of stimuli, when the participant should use cognitive functions of information processing to remember the target stimuli, make comparisons between the target and non-target stimuli that will appear on the screen, and react pressing the button if the target stimuli were presented, or inhibit this behavior if the non-target were presented. The greater alpha-power in the moment 1 and 3 (0,5s before the stimulus presentation) may be associated to the expectancy of appearance of stimuli, while the alpha-power in the moments 2 and 4 (0,5s after the stimulus presentation) can be related to the reaction to press the button. Alpha-power is also elicited in situation where subjects withhold or control the execution of a response and it is obtained over sites that probably are under or exert top-down control (De Carvalho *et al*., 2013).

The results presented by PD patients of lower absolute alpha-power in the moment 3 (the first moment observed after the film presentation) in the electrodes Fp1, F3, Fz, P4,

Pz, T3 and T6 points the influence of the ansiogenic film, increasing the anxiety and the information processing, decreasing the power of alpha. This way, these patients could have impairment on the accuracy of working memory to execute the *oddball* task after the exposition to the VR movie. It is not only an excessive cognitive processing, but this phenomenon resembles to a kind of *emotional blindness*, when the acute anxiety interferes on the information processing and on the descriptive ability. This increase on the moment 3 happened with the HC only for the T3 electrode.

This emotional blindness can affect the performance on the task execution, just like these patients can experiment on their common lives the difficulty to percept, process and discriminate information when under the influence of anxiety.

At the same time that the increase of alpha power represents a relaxed condition, it is also associated with a low excitability state (Cahn and Polich, 2006; Gordeev, 2008; Pavlenko *et al*., 2009). We can't affirm that occurs a relaxing during the execution of the task, even because after the presentation of the movie, but we can say that probably the task loses the capacity to increases the excitability so far the blocks of the task are been done.

Frontal brain asymmetry is considered a trait marker related to psychopathology as well as a state marker associated with acute emotional reactions (Davidson *et al*., 1990; Wiedemann *et al*., 1999). In our results we could observe an interaction between the factors over the frontal area only in the left electrodes (Fp1, F3 and F7 electrodes), while occurred the opposite over the parietal area (P4 electrode). The fact to belongs to a group of PD patients, realize an *oddball* task that involves working memory and decision making, and watch an ansiogenic VR movie interferes on the left frontal region and right parietal region.

What is the role of the left frontal region in this context of working memory after the contact with a VR movie that induces anxiety? The received information needs to be processing and sent to the frontal region for a decision making to be done. This interference of higher alpha power could be related to the abnormal processing of PD patients. There are different models of brain asymmetry for emotional processing (Goldstein, 1939; Davidson, 1995; Demaree *et al*.,2005). A long time ago, Goldstein (1939) showed that damage to the left hemisphere was more likely to cause a catastrophic-depressive reaction in psychiatric patients than damage to the right hemisphere. The left brain hemisphere is associated with emotional processing and we

assumed that anxiety or negative emotions affected the alpha-power activity in this region. The left hemisphere express more clearly the relationship between the cognitive and emotional aspects, as the execution of a cognitive task influenced by an ansiogenic movie and the fact to be a PD patient interferes reflects this hemisphere activity.

In a preview study (Silva *et al*., 2017), we observe that the left frontoparietal network were the only area affected by the VR movie, with a gamma coherence increase after the computer simulation movie; demonstrating a left frontoparietal participation in the processing of ansiogenic stimuli. Our result of this present study observed a left frontal participation of absolute alpha-power during the execution of a working memory task after the induction of anxiety.

Our results of interaction over the temporal electrodes (T4, T5 and T6) evidence the interference of anxiety during an *oddball* task in the temporal region. The temporal cortex has an important correlation with the limbic system activity, mainly with the amygdala activity (LeDoux, 1992). In turn the amygdala plays a special central role in fear learning processes, being the a center where different impulses converge, what conducts excitatory efferent outputs to the hypothalamus, midbrain and brainstem areas, which thereafter select suitable behavioral and autonomic programs (Globish *et al*., 1999; De Carvalho *et al*., 2013). The lower absolute alpha-power over the temporal area should be associated with increased temporal activation.

Our RT results were already described in a preview paper (Silva *et al*., 2017). The behavioral analysis of reaction time (RT) demonstrated that PD patients were faster than HC in the *oddball* task. What lead us to the questioning if the faster reactivity to PD could be related to the high excitability to new stimuli and symptoms related to PD. In a preview study, researchers investigated the limits of the perception of PD patients asking them to recognize panic related words next to neutral words (Pauli *et al*., 1997). They observed a significantly faster RT in PD patients when to HC. This result could indicate an explicit memory bias of PD patients for anxiety related stimuli (Pauli *et al*., 1997). This may be related to the cognitive model of PD, which explains the dysfunctional misinterpretation of external stimuli (Pauli *et al*., 1997) and bodily sensations (Clark, 1986) as signs of confirmation of the danger potential of the present situation or stimuli.

Our results pinpoint the interference of anxiety in RT and loss of precision. High levels of anxiety in patients with PD could affect cognitive functioning (Castillo *et al*.,

2010). The excitement and anxiety could lead to a loss of selective attention, which mediates the process of encoding information and support received (Dratcu and Bond, 1998). Thus, these patients have a faster reactivity that is not accompanied by accuracy of the information processing. This could be explained by the fact that impulsivity is higher in patients with anxiety disorders than in HC (Perugi *et al*., 2011).

Conclusion:

Alpha power of PD patients was reduced during the increased information processing associated with the computer simulation. Our results confirm our hypothesis that the PD patients present a lower absolute alpha power when compared to healthy controls when under an ansiogenic situation. The results showed a significant difference between the moments, since the absolute alpha-power was growing over the advance of the moments. We supposed that the task loses the capacity to increases the excitability so far the blocks of the task are been done. The lower absolute alpha-power observed in the moment 3 (just after the film presentation) can reflect the ansiogenic potential of this VR movie, since it increases the anxiety and the information processing, causing a decrease in the alpha oscillation. Our result of higher left frontal absolute alpha-power during the execution of a working memory task (after the induction of anxiety) highlights that the ansiogenic VR movie interferes on these area activity. This interference of higher alpha power could be related to the abnormal processing of PD patients. The reaction time results showed that PD patients were faster than HC in the *oddball* task, what could be related to the high excitability to the symptoms related to PD.

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Capítulo V – Conclusão

Os dados e os artigos sintetizados na presente dissertação tiveram como objetivo elucidar alterações eletrofisiológicas encontradas em pacientes com TP. No primeiro artigo, foram apontadas diferenças no comportamento do componente do P300 em pacientes, o que pode estar relacionado com alterações no processo cognitivo de respostas automáticas a novos estímulos, contribuindo para a excessiva reatividade e excitabilidade da ansiedade diante de ambientes com alta carga sensitiva, uma vez que ocorre um foco exagerado nos estímulos relacionados com o transtorno. As alterações encontradas no componente P300 corroboram os sintomas de interpretações inadequadas de sinais ambientais e internos como perigosos e catastróficos, o que poderia estar relacionado como uma falha na inibição automática a novos estímulos ou falha na modulação de respostas mais conscientes e sofisticadas. Tais informações podem se relacionar com os dados encontrados na presente pesquisa experimental, por meio da qual foram elaborados os outros dois artigos que descreveram alterações eletrofisiológicas em pacientes com TP no domínio da frequência.

O artigo II apontou, através da análise da coerência em gama, que a comunicação cerebral na rede frontoparietal esquerda foi a única área que sofreu influência do filme de RV, com um aumento após a sua apresentação, demonstrando a participação desta região no processamento de estímulos ansiogênicos, o que não apareceu na rede frontoparietal direita. A menor coerência gama encontrada nos pacientes nas áreas frontais e parietal pode contribuir para o prejuízo na comunicação cerebral no TP, o que se expressaria em um desempenho inferior na execução da tarefa *oddball*, no prejuízo no processamento e modulação de estímulos relacionados a sensações corporais (de maneira catastrófica). Entretanto, também foram encontrados dados contrários à hipótese inicial, pois pacientes com TP apresentaram maior coerência em gama em dois pares de eletrodos, o que pode estar de acordo com uma possível interferência ("*noise*") na comunicação entre as áreas cerebrais e, consequentemente, no processamento de informações.

O artigo III demonstrou menor potência absoluta de alfa durante a tarefa *oddball* em pacientes com TP, quando comparados a sujeitos saudáveis na região frontal, parietal e temporal. Entendeu-se que essa diferença ocorreu devido à maior presença de ansiedade durante sua execução e pode estar relacionada à dificuldade destes pacientes na regulação da excitabilidade de regiões subcorticais e na inibição de estímulos

irrelevantes, causando dano nas funções *top-down*, afetando o processamento adequado de informações por esses pacientes, sobretudo de estímulos relacionados com a sintomatologia do TP. Outro resultado importante foi o de menor potência absoluta de alfa em pacientes com TP após a apresentação do filme de RV, aumentando o processamento de informação e diminuindo a oscilação de alfa. Neste sentido, os pacientes podem apresentar não apenas um processamento cognitivo excessivo, como uma forma de "cegueira emocional". Esta interferência pode ocorrer no desempenho de tarefas, tal como estes indivíduos podem vivenciar dificuldade, em seu dia a dia, na percepção, processamento e discriminação de informações quando sob a influência da ansiedade.

A análise comportamental do tempo de reação demonstrou que os pacientes com TP foram mais rápidos na resposta da tarefa *oddball*. Apesar da análise da quantidade de erros não ter sido realizada, esta alta reatividade pode estar relacionada com a alta excitabilidade diante dos estímulos e sintomas relacionados com o transtorno, além da perda de acurácia no desempenho das tarefas que exijam funções executivas complexas devido à presença de ansiedade.

Estes estudos contribuem para o conhecimento das alterações neurofisiológicas do TP durante a realização do paradigma oddball, algo que ainda não havia sido realizado. Este paradigma envolve uma tarefa que demanda atenção e memória de trabalho, o que torna possível o aprofundamento do conhecimento eletrofisiologico e das alterações cognitivas presentes no TP. Os resultados ajudam a avançar com o conhecimento na área da pesquisa e da clínica, uma vez que aponta a necessidade de buscar meios de minimizar tais prejuízos, seja por intervenção medicamentosa, psicoterapia ou técnicas de reabilitação cognitiva. Além disso, também elucida a necessidade do profissional em contato com estes pacientes compreender que a sintomatologia do TP pode ir muito além dos já descritos no DSM-V.

Apesar dos resultados encontrados, podemos identificar algumas limitações apresentadas pelo estudo, como o pequeno número de pacientes e controles recrutados para o estudo, além da necessidade de relacionar os dados eletrofisiológicos encontrados com os resultados de testes neuropsicológicos que avaliassem funções executivas. Para a possibilidade de generalização dos resultados, se faz necessário o aumento deste número de participantes. Ainda há muito a ser pesquisado na área de eletrofisiologia de transtornos de ansiedade, então futuras pesquisas deveriam buscar investigar as diferenças neurobiológicas e neuropsicológicas entre pacientes com TP e sujeitos

saudáveis, mas também a eficácia de tratamentos medicamentosos e/ou psicoterapêuticos para minimizar tais diferenças.

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Lista de Anexos:

Anexo I – Termo de Consentimento Livre e Esclarecido

FORMULÁRIO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto: Alterações eletrofisiológicas em pacientes com transtorno de pânico medidas por meio de um vídeo de realidade virtual e pela tarefa *oddball*.

Declaração de Idade: Eu declaro que tenho mais que 18 anos e que participarei do projeto de pesquisa conduzido por Luiza Wanick Di Giorgio Silva, sob orientação do Prof. Dr. Bruna Brandão Velasques, no setor de Mapeamento Cerebral e Integração Sensoriomotora – IPUB/UFRJ.

Objetivo: Eu entendo que o objetivo deste projeto é observar possíveis alterações corticais desencadeadas pela tarefa de atenção e vídeo formado por situações ansiogênicas.

Procedimentos: Os procedimentos deste projeto requerem uma visita ao setor de Mapeamento Cerebral e Integração Sensoriomotora (IPUB/UFRJ), onde serei submetido à tarefa de apresentação de estímulos visuais, à um vídeo de Realidade Virtual e à captação simultânea do sinal eletroencefalográfico (EEG). O experimento terá duração estimada de 1 hora.

Riscos: Eu entendo que o vídeo de realidade virtual pode desencadear alguns sntomas de ansiedade.

Confidencialidade: Eu entendo que todas as informações coletadas no estudo são confidenciais e que meu nome não será divulgado em momento algum. Entendo ainda que toda e qualquer informação será utilizada somente para fins acadêmicos.

Benefícios: Eu entendo que o desenvolvimento deste projeto e minha participação não me trarão qualquer benefício pessoal.

Liberdade para interromper a participação: Eu entendo que a qualquer momento posso pedir para interromper minha participação na realização do presente estudo e que, se assim eu desejar, a responsável pelo estudo irá fornecer os resultados da minha participação em uma oportunidade futura.

Identificação da responsável pelo estudo:

Prof. Dr. Bruna Brandão Velasques: Orientador
Setor de Mapeamento Cerebral e Integração Sensoriomotora
Instituto de Psiquiatria - Universidade Federal do Rio de Janeiro (IPUB/UFRJ)
Av. Venceslau Brás, 71 – Fundos – Botafogo
Rio de Janeiro – RJ, 22.780-160
Fone: (21) 2295-3449

_____	_____
Nome do Participante	Data de Nascimento
_____	_____
Assinatura do Participante	Data

Anexo II – Questionário Informativo

Questionário Informativo

I- Dados Demográficos

Nome:
Endereço:
CEP:
Telefone Residência: Telefone Celular:
Telefone Recado: Falar com:
E-mail:
Idade: Gênero: F M
Grau de Escolaridade:
Anos de Estudo:
Situação ocupacional:
Renda individual: Renda familiar:
Estado Civil:
Naturalidade:
Cor:
Religião:

II- Hábitos
Tabagismo: ( ) sim ( )nunca ( ) apenas no passado
Se SIM ou no PASSADO: Quanto tempo: Cigarros por dia :
Tempo de parada:
III- Dados clínicos e terapêuticos

Comorbidades clínicas: ( ) sim ( ) não
Doenças neurológicas:
Doenças Cardiovasculares:
Doenças Pulmonares:
Doenças Gastroenterológicas:
Doenças Nefro-urológicas:
Doenças Osteo-articulares:
Doenças Reumatológicas:
Doenças Dermatológicas:
Doenças Metabólicas:
Doenças Imunológicas:
Outras doenças:
Tratamento: ( ) sim ( )não
Se sim, quais medicamentos:
Doença crônica: ( ) sim ( ) não

IV- Sobre o TP

Idade de início:
Data do diagnóstico:
Agorafobia:

Tratamento psicológico anterior:
Especificar tratamento:
Tratamento psicológico atual:
Tratamento psiquiátrico anterior:
Especificar tratamento:
Uso medicamentoso atual:
Uso medicamentoso anterior:
Portadores de Transtornos psiquiátricos na família:
Especificar transtorno e parentesco:

Anexo III – Questionário sobre Realidade Virtual - IPQ

Instituto de Psiquiatria – IPUB/UFRJ
Laboratório do Pânico e Respiração

Questionário sobre Realidade Virtual - IPQ

Responda as perguntas abaixo em relação à experiência pela qual passou. Marque um X sobre o quadrado que responde mais adequadamente as perguntas.

1- O quanto você estava ciente do entorno do mundo real enquanto navegava no mundo virtual (sons, temperatura da sala, outras pessoas etc)?

-3	-2	-1	0	+1	+2	+3
extremamente ciente		moderadamente ciente				nada ciente

2- Quão real o mundo virtual pareceu para você?

-3	-2	-1	0	+1	+2	+3
nada real		moderadamente real				completamente real

3- Eu tive a sensação de agir dentro do espaço virtual, ao invés de operar algo pelo lado de fora.

-3	-2	-1	0	+1	+2	+3
discordo totalmente						concordo totalmente

4- Quanto a sua experiência no mundo virtual pareceu consistente com sua experiência no mundo real?

-3	-2	-1	0	+1	+2	+3
não consistente		moderadamente consistente				muito consistente

5- Quão real o mundo virtual pareceu para você?

-3	-2	-1	0	+1	+2	+3
tão real quanto um mundo imaginário						indistinguível do mundo real

6- Eu não me senti presente no espaço virtual.

-3	-2	-1	0	+1	+2	+3
não me senti presente						me senti presente

7- Eu não estava ciente do meu ambiente real.

-3	-2	-1	0	+1	+2	+3
discordo totalmente						concordo totalmente

8- No mundo gerado por computador eu tive a sensação de “estar lá”.

-3	-2	-1	0	+1	+2	+3
nenhuma						muita

9- De alguma forma eu senti que o mundo virtual me envolveu.

-3	-2	-1	0	+1	+2	+3
discordo totalmente						concordo totalmente

10- Eu me senti presente no espaço virtual.

-3	-2	-1	0	+1	+2	+3
discordo totalmente						concordo totalmente

11- Eu continuava prestando atenção ao ambiente real.

-3	-2	-1	0	+1	+2	+3
concordo totalmente						discordo totalmente

12- O mundo virtual pareceu mais realista que o mundo real.

-3	-2	-1	0	+1	+2	+3
discordo totalmente						concordo totalmente

13- Eu senti como se eu estivesse apenas percebendo imagens.

-3	-2	-1	0	+1	+2	+3
concordo totalmente						discordo totalmente

14- Eu estava completamente capturado pelo mundo virtual.

-3	-2	-1	0	+1	+2	+3
discordo totalmente						concordo totalmente