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ERROR-RELATED NEGATIVITY (ERN) AS A TRANSDIAGNOSTIC
ENDOPHENOTYPE FOR IRRITABILITY TRAITS IN A COMMUNITY SAMPLE: A
RDoC PERSPECTIVE

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"We learn from failure, not from success!"

Bram Stoker

"It is unwise to be too sure of one's own wisdom. It is healthy to be reminded that the strongest might weaken and the wisest might err."

Mahatma Gandhi

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"The essence of all beautiful art is gratitude."

Friedrich Nietzche

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ABSTRACT

Mental disorders present difficulties in the research of their mechanisms, considering the high levels of comorbidity and the lack of specific neuroscience data to evaluate them. Estipulating deficit circuits in the disorders and the best treatment is a complex task, given the limited comprehension of the factors that correlate to the disorders. The utilization of biomarkers has proved an efficient and reliable alternative to provide precise diagnosis. Among the biomarkers, the Error-Related Negativity component, an event-related cortical potential, has presented high indexes of stability and validity in correlating to anxiety, obsessive, and mood-related mental disorders. The present dissertation evaluated irritability traits in a community sample, using a Flanker task, that has consistently elicited Error-Related Negativity according to the literature. Our results corroborate literature and found a frontocentral negativity, that peaked around 100ms after the commission of an error in the Flanker Task. However, our manipulation of negative feedback did not support literature, and ERN amplitudes were less enhanced post negative feedback. The relationship between irritability and ERN remains unclear. Future studies should, therefore, address these questionings.

Keywords: Biomarkers; Error-Related Negativity; Irritability; *Flanker.*

INTRODUCTION

Mental disorders represent complex targets for research, since they manifest in different ways and are frequently comorbid with one another (Weinberg et al., 2015). Distinct mental disorders involve multiple dysfunctions in putative mechanisms, such as exaggerated fear and deficient impulse control, and different disruptive mechanisms play a role in distinct disorders (Sanislow et al., 2010).

The diagnosis of mental disorders, according to the current diagnostic manuals, the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM), is based on clinical observation, self-report and analysis of symptoms, failing to associate such data to the developments in the field of clinical neuroscience and genetics (Insel et al., 2010). The Diagnostic and Statistical Manual of Mental Disorders, in its fifth edition (DSM 5) (American Psychiatric Association, 2013), though proposing a less categorical classification of mental disorders, maintains the previous editions pattern of basing on a nosologic model, in which mental disorders follow a medical model of diseases as a set of identifiable symptoms (Leon, 2014).

Due to the nosonomic logic applied to diagnoses, the traditional diagnostic manuals (DSM and ICD) present fragilities in separating comorbid disorders and limitations on the ability to predict response to treatment (Insel et al., 2010). The co-occurrence of multiple mental disorders may reflect different patterns of symptoms that result in shared risk factors and maybe the same underlying disease process (NIMH, 2008). Nevertheless, the advance of neuroscience in finding circuits that refer to the difficulties in mental disorders and the progress of genetics in associating candidate genes to disorders, these findings have not yet been incorporated by diagnostic manuals. Psychiatry is an area of Medicine that only recently has resorted to neuroscience tools for performing diagnoses and that presents fragile capacity to predict response to treatment and to make decisions regarding the appropriate treatments (Sanislow et al., 2010).

As a response to those difficulties, the National Institute of Mental Health (NIMH) launched, in 2008, the Research Domain Criteira (RDoC), a project destined to create a structure for research in pathophysiology, along with genetics and neuroscience, that will futurally inform schemes for classifying mental disorders (Insel et al., 2010). The basic premise of RDoC is that mental disorders are brain circuits disorders (NIMH, 2008). The RDoC paradigm is constructed as a matrix, in which specific domains (i.e. negative valence systems, positive valence systems, cognitive systems, social processes and arousal and

regulatory systems) are evaluated from units of analysis, composed by genes, molecules, cells, circuits, physiology, behavior, self-report and paradigms. Thus, it adopts a dimensional logic of mental disorders, considering each component that integrates them, their relationship to other disorders and their development over the life-span. For this reason, the RDoC classification assumes that dysfunctions in neural circuits can be identified with the tools of clinical neuroscience, including electrophysiology, functional neuroimaging and new methods of quantifying in vivo connections. These genetic and clinical neuroscience data will lead to biosignatures that will amplify clinical symptoms and signals for clinical conduct (Insel et al., 2010).

The RDoC project does not break with the classification proposed by DSM and ICD and is still configured as a research project, not suitable for clinical diagnoses. However, it suggests the utilization of neuroscience tools by researchers and the incorporation of these data on mental health research.

Irritability in DSM-5

Irritability is described in the literature as a state composed of unpleasant emotion, negative valence and a high level of brain arousal (Ford et al., 2010, 2012) and as a proneness to anger (Salum et al., 2016). An angry state is defined as an emotional state marked by subjective feelings that vary in intensity from medium irritation to intense fury (Wilkowski & Robinson, 2008). Anger as a trait, on the other hand, involves individuals' differences that are stable in frequency, duration and intensity of the anger state (Wilkowski & Robinson, 2008). Extreme levels of anger are a central characteristic in different mental disorders, including mood disorders (Bipolar Disorder, Major Depressive Disorder, among others) and personality disorders (Borderline, Narcissistic and Paranoid) (Wilkowski & Robinson, 2008).

Anger attacks and chronic irritability can be conceptualized as an exaggerated reactivity to emotional stimuli, presenting anger as the affective component and aggression as the behavioral one (Caprara, 1985). Thus, they are characterized as presenting a reduced threshold for experimenting negative affects in reponse to frustration (Ryan, 2013)

In DSM, irritability has been historically presented as a symptom in several disorders, however, few diagnoses evaluate anger state and trait as a particular disorder. In its fifth edition, though, DSM proposes the incorporation of Disruptive Mood Dysregulation Disorder (DMDD) as a clinical condition where irritability is the symptom with higher significance. Both DMDD and Intermittent Explosive Disorder (IED), previously incorporated on DSM, are characterized by recurrent and severe anger explosions that manifest by language (i.e.

verbal violence) and/or behavior (i.e. physical aggression to people or property) and are considered disproportionate in intensity or duration to the situation or provocation; difficulty controling aggression; and significant clinical suffering, as the individual remains in an irritable mood for a long period after the explosion (APA, 2013).

In the literature, irritability is described as humor, having aggression as its behavioral component (Caprara, 1985). Irritability is an internal state tipically associated to a motivation to harm others, whilst aggressiveness is the act of harming others (Wilkowski & Robinson, 2008). Aggressiveness, though, is divided in pro-active and reactive. In the first one, the individual presents accentuated offensive behavior, taunting conflict situations, which is characteristic of Oppositional Defiant Disorder (ODD) and Conduct Disorders (CD), for example. In the second one, subjects present aggressive reaction to the provocations or conflict situations, indicating lower inhibitory control and impulse control (White, 2014), as evidenced by DMDD and IED.

Individuals with high irritability present difficulties disengaging attention from negative stimuli and tend to interpret environmental clues in a hostile way. Thus, they present reduced inhibitory control, associated to a smaller activation of the prefrontal part of the cortex, measured by neuroimaging studies (Wilkowski & Robinson, 2008). Inhibitory control is negatively correlated to anger behavioral signs in frustrating situations, as cognitive tasks, for example. Emotional self-regulation, on the other hand, refers to the ability of modulating emotion, cognition and behavior for goal seeking (White, 2014). Therefore, one way of measuring self-regulation is through executive functions tasks, in which there is a control component for goal seeking and the need to inhibit dominant behaviors and maintaining attentional focus on the task, even without motivation (White, 2014).

Error-Related Negativity (ERN) in individuals with irritability traits

Error monitoring consists in signaling and detecting mistakes, with the aim to optimize behaviors between a range of tasks and situations. Such monitoring function is an essencial component of behavioral regulation (Moser et al., 2013). Error-Related Negativity (ERN) is a component of Event-Related Potentials (ERP) that reaches maximum amplitude of negativity in frontocentral regions between 50ms and 100ms after the commission of an error in simple reaction time tasks. This measure demonstrates the exact moment in which the error committed is detected by the dorsal portion of the Anterior Cingulate Cortex (ACC) and allows the individual to adapt and continue the task (Olvet & Hajcak, 2008; Hajcak et al., 2012; Moser et al., 2013), and has been identified as a useful and realiable measure of partial

and total detection of errors in healthy and clinical participants (Zambrano-Vazquez & Allen, 2014).

Several studies point out the ERN as an endophenotype for mental disorders, identifying this wave as capable of measuring traits and not only states, being reliable in contexts where the participant might not be presenting the symptom to be studied (anger, for example) (Olvet & Hajcak, 2008). The technique of registering brain waves, electroencephalography (EEG), is appropriate for the evaluation of mental disorders, since it is highly tolerated by kids, adults and elders, does not offer risks or discomfort, remains stable over time in the same individual and offers distinct registers, in adittion to providing excellent time resolution. Thus, it is configured as an adequate biomarker for studies in psychiatry (Kappenman & Luck, 2015).

In their metanalysis, Moser and colleagues (2013) evaluated studies conducted with the ERN and the associated psychiatric conditions. There were found hundreds of studies involving the ERN and anxiety disorders, schizophrenia, substance abuse, personality disorders, among others. However, we have no knowledge of any study that has evaluated irritability disorders with the ERN as an electrophysiological marker.

Due to the reduction of inhibitory control in individuals with high irritability and the biomarker character of the ERN, the study of this component in individuals with irritability traits might offer answers and clarify the mechanisms that underlie irritation. Literature recognizes enhanced amplitudes of ERN in individuals with anxiety and, not consensually, depression, so that we can hypothesize that these deflections occur due to an underlying mechanism, that could be comprehended as negative affect (Olvet & Hajcak, 2008). Thus, is it possible to infer that irritability, also part of the negative affect construct, might present differences in the ERN amplitudes, compared to healthy individuals.

ERROR-RELATED NEGATIVITY (ERN) AS A TRANSDIAGNOSTIC ENDOPHENOTYPE FOR IRRITABILITY TRAITS IN A COMMUNITY SAMPLE: A RDoC PERSPECTIVE

ABSTRACT

Error-related negativity (ERN), a frontocentrally deflection appearing between 50-100 ms after the commission of an error, is considered a reliable endophenotype for mental disorders, being associated to several diseases. In RDoC's matrix, it is considered as an unit of analysis in three domains: sustained threat, performance monitoring and reward learning. In this study, we aimed to evaluate the ERN as an endophenotype for irritability traits in ten adults, with heterogeneous symptoms, of a community sample. Subjects were submitted to an adapted Flanker task and received increasingly aversive negative feedback at the end of each block, starting on block 4 of 7. Our findings suggest that the number of errors increased after the introduction of negative feedback, but reaction times and ERN amplitudes diminished, casting doubt about the direction of performance monitoring in irritability. This validates the idea of ERN as a transdiagnostic endophenotype, suitable for neuroscience and diagnostic research. Keywords: error-related negativity, Flanker task, irritability.

Since Kraepelin's (1896/1987) concepts of mental disorders, psychiatry has been finding difficulties in associating the traditional model of diagnoses based on clinical observation and clustering of symptoms to the discoveries of empirical research and clinical neuroscience (Insel et al.,, 2010; Sanislow et al., 2010). Diagnostic categories based upon presenting symptoms and signs fail to discover the mechanisms that underlie mental disorders and might be slowing the development of new treatments. To address this issue, the National Institute of Mental Health (NIMH) has launched, in 2008, the Research Domain Criteria (RDoC) project, aiming to "incorporate data on pathophysiology in ways that will eventually help identifying targets for treatment development, detect subgroups for treatment selection, and provide a better match between research finding and clinical decision making" (Insel et al., 2010, p.748).

The RDoC premise is that mental disorders are disorders of brain circuits and can be identified through neuroscience tools, such as brain imaging, electroencephalography and in vivo connections (Insel et al., 2010). The RDoC framework is composed by a matrix, divided in five domains (i.e. negative valence systems, positive valence systems, cognitive systems,

social processes and arousal and regulatory systems) and eight units of analysis (i.e. genes, molecules, cells, circuits, physiology, behavior, self-report and paradigms). Thus, research according to RDoC approach is encouraged to study mechanisms in a transdiagnostic way, in order to elucidate the process underlying the disorders (Sanislow et al., 2010). From this perspective, research focusing on brain mechanisms and neural responses fits well within the RDoC matrix (Weinberg et al., 2015).

Error-Related Negativity and the RDoC approach

The ability to detect errors and adapt behavior is essencial to a changing-environment, therefore, is a fundamental brain capacity for human beings (Hajcak et al., 2012; Riesel et al., 2013; Weinberg et al., 2015). Error-Related Negativity (ERN) is a fronto-centrally maximal negative deflection in the Event-Related Potential (ERP) that reaches maximum amplitude between 50ms and 100ms after the commission of an error in simple reaction time tasks, even before conscious awareness (Hajcak et al., 2012; Hanna & Gehring, 2016; Weinberg et al., 2015, 2016). This wave was firstly discovered in the 1990's by two independent teams. In Germany, it was discovered by Falkenstein (1991) and called Error Negativity (Ne) and in the United States it was found by Gehring (1993) and called Error-Related Negativity (ERN) (Weinberg et al., 2015). From its discovery in the early 1990s until this day, the Error-Related Negativity (ERN) remains the most widely investigated electrophysiological index of cortical error processing (Wessel, 2012).

The Anterior Cingulate Cortex appears to be the main generator of ERN, as evidenced by multiple lines of research (Hajcak et al., 2012; Hanna & Gehring, 2016; Olvet et al., 2008; Weinberg et al., 2015, 2016). It is particularly important in the RDoC framework, since abnormalities in performance monitoring have been implicated in multiple forms of psychopathology (Riesel et al., 2017).

The ERN has shown to be a valid and reliable tool for measuring traits and a promising candidate for biomarker on psychiatric disorders (Kappenman & Luck, 2015; Olvet & Hajcak, 2008). It has been exhaustively studied across different levels of task difficulty and modalities, across the life-span in children as young as 5 years old and in adults as old as 80 years old, and in most psychiatric disorders (Hanna & Gehring, 2016; Weinberg et al., 2015).

Empirical findings consistently suggest that enhanced ERN amplitudes are associated with anxiety and some inconclusive research point depression as a diagnosis marked by enhanced error-monitoring, indicating that high amplitudes on ERN might reflect an endophenotype of negative affect disorders (Weinberg et al., 2015). In the RDoC framework,

though, the ERN appears as the physiology unit of analysis in three domains (Cognitive Control – Performance Monitoring; Negative Valence Systems – Sustained Threat; and Positive Valence Systems – Reward Learning) indicating that the ERN reflects variance in each of these domains and functionally integrates both cognitive and motivational factors (Hanna & Gehring, 2016). Of particular interest of this article is the construct "sustained threat" of the negative valence systems domain.

Negative Valence Systems – Sustained Threat

"An aversive emotional state caused by prolonged (i.e., weeks to months) exposure to internal and/or external condition(s), state(s), or stimuli that are adaptive to escape or avoid. The exposure may be actual or anticipated; the changes in affect, cognition, physiology, and behavior caused by sustained threat persist in the absence of the threat, and can be differentiated from those changes evoked by acute threat." Definition provided by the RDoC working group convened to establish Negative Valence Systems.

Comitting errors can be dangerous and, in almost every case, mistakes require attention and corrective action (Weinberg et al., 2015). Errors can be associated to exogenous threats (i.e. physical danger) or endogenous threats (i.e. not related to an environment threat, such as academic performance or feedback). In their article, Weinberg et al (2016) discuss the inclusion of the ERN as part of the sustained threat domain and propose that enhanced ERN amplitudes are only caused by endogenous threats. The authors argue that rather than reflecting the degree of instantiated cognitive control, the magnitude of the ERN varies according to within- and between-subjects variables that impact the evaluation of errors. The ERN would reflect, then, the degree to which errors are considered threatening (Weinberg et al., 2016). According to their hypothesis, that could explain why negative affect disorders are more suscetible to enhanced ERN.

Negative Feedback and Error-Related Negativity

Individuals require frequent feedback from the environment in order to adapt behaviour toward the success of their actions. Relevant feedback, in those cases, must comprise both valence (i.e. a good or bad outcome) and magnitude (how good and how bad was the performance/outcome) (Hajcak et al., 2006). Feedback can also explicit whether a goal was reached or not and it is highly associated with expectancy. Unexpected negative events produce enhanced brain waves than expected ones (Holroyd et al., 2006).

To measure the effects of feedback in the brain, an ERP component, the feedback Error-Related Negativity (fERN) is highly studied. This negative deflection is distributed over

frontal areas of the scalp and peaks at approximately 250ms following the onset of negative feedback stimuli (Hajcak e al., 2006; Holroyd et al., 2006). Interestingly, fERN is only associated to negative feedback, indicating that an undesirable outcome has occurred, and is not associated with positive feedback, suggesting that the system that produces this component is diferentially sensitive to positive and negative feedback (Holroyd et al., 2006). The amplitude of the fERN depends on both the valence and the expectedness of the outcome, such that largest fERNs are elicited by relatively unexpected negative events (Holroyd et al., 2006). Studies have been conducted manipulating the magnitude of gain and loss of participants on tasks and results suggest that the evaluative system that produces fERN treats neutral and negative feedback stimuli in much the same way (i.e. the brain considers two possible outcomes: gaining or not gaining, which indicates that neutral feedback is negative) (Hajcak et al., 2006; Holroyd et al., 2006).

The fERN reflects a component of a neural mechanism that underlies how humans learn to pursue reward and avoid punishment (Holroyd et al., 2006) and is intimately related to reward learning. Reward learning is defined by RDoC's cognitive control research working group as: "A process by which organisms acquire information about stimuli, actions, and contexts that predict positive outcomes, and by which behavior is modified when a novel reward occurs or outcomes are better than expected. Reward learning is a type of reinforcement learning, and similar processes may be involved in learning related to negative reinforcement".

Ford and colleagues (2010, 2012) have demonstrated that individuals with higher irritability traits are attentionally biased towards prizes and rewards and Wilkowski and Robinson (2008) suggest that angry individuals are more intolerant to frustration. Due to these aspects, the introduction of neutral and negative feedback between blocks, unrelated to the participants actual performance, may mislead the reward learning system and generate more frustration and enhanced error related negativity in individuals with higher irritability traits, consisting in an interesting measure of the effect of feedback in clinical populations.

Goals

The main goal of this study was to analyze the relationship between irritability and attentional processes, such as error monitoring, in adults from a community sample. Specific goals were to evaluate the presence of irritability and error related negativity amplitudes, before and after the introduction of negative performance feedback, and to relate those measures to accuracy and reaction time on the experimental task and to self-reported psychiatric symptoms.

Hypothesis

We hypothesized that individuals with higher irritability traits would present longer reaction times and inferior accuracy on the experimental task, suggesting reduced inhibitory control and higher impulsivity of this population, especially after experimental manipulation of negative feedback. This feedback would likely eliciate frustration responses, less tolerated by individuals with high irritability, culminating in enhanced ERN waves. We expected to find differences in the magnitude of ERN waves for individuals with low and high irritability. If irritability is related to enhanced error monitoring and longer reaction time on experimental tasks, indicating the interference of emotion on cognitive performance, the study of irritability might be an interesting tool for future treatment with irritated populations and follows RDoC guidelines for studying mental disorders.

METHOD

Participants

Ten adults (6 female), belonging to a community data bank of the research group "Negative Affect and Social Processes", supervised by Giovanni Salum, M.D., PhD at the Hospital de Clínicas de Porto Alegre (HCPA), participated in this study. Participants were the parents of children previously evaluated in another research project and had no relationship to the Hospital. Subjects were contacted by telephone and invited to come to the hospital to be part of the experiment. The study was previously approved by the ethics committee of the Hospital (Appendix A). All participants received verbal and written information about the aims and procedure of the study and written consent was obtained (Appendix B). All participants had normal or corrected-to-normal vision and reported no history of head trauma or neurological disease. No participant had used alcohol, any kind of drug or ingested caffeine 4 hours before the experiment, as requested by the researcher when scheduling the interview and as measured by a questionnaire. All participants were right-handed. The mean age was 37.80 years (SD =12.14). 70.0 % of the sample was Caucasian, 10% was Black, 10% was Asian and 10% was grayish-brown. The average of the individual income at a monthly basis was R$ 1180.00 (SD = 1247.93). A Socio-Demographic and General Health Questionnaire was filled by all participants (Appendix C), and relevant information can be observed in Table 1. Only one participant was medicated with psychotropics (fluoxetine). All participants were evaluated for psychiatric diagnoses through an adapted version of Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan, 2002) for DSM-5. Presence of diagnoses can be observed in Table 2.

Table 1. Sample Characterization in Terms of Educational Levels

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Complete Elementary School	2	20.0	20.0	20.0
	Incomplete High School	2	20.0	20.0	40.0
	Complete High School	1	10.0	10.0	50.0
	Incomplete Undergraduate Studies	4	40.0	40.0	90.0
	Complete Post-Graduation	1	10.0	10.0	100.0
	Total	10	100.0	100.0	

Table 2. Presence of diagnosis evaluated through M.I.N.I.

		Frequency	Percent
Valid	PD	0	0
	A	2	20
	SP	0	0
	GAD	2	20
	MDD	1	10
	SR	0	0
	HM	1	10
	OCD	0	0
	PTSD	1	10
	AA	1	10
	PS	0	0
	ADHD	5	50

Label: PD=Panic Disorder; A=Agoraphobia; SP=Social Phobia; GAD=Generalized Anxiety Disorder; MDD= Major Depressive Disorder; SR= Suicide Risk; HM=Hypo(Mania); OCD= Obsessive-Compulsive Disorder; PTSD= Post-Traumatic Stress Disorder; AA= Alcohol Abuse; PS= Psychotic Syndrome; ADHD= Attention Deficit Hyperactivity Disorder

Instruments and Materials

- Socio-Demographic and General Health Questionnaire. This instrument was developed for this study and evaluates data such as age, gender, educational levels and general health conditions that might affect the participant's performance. (Appendix B).

- *Mini International Neuropsychiatric Interview* -M.I.N.I (Sheehan et al., 2002). This instrument is a standardized diagnostic interview, adapted for DSM-5, which explores the main psychiatric disorders.

- *Positive and Negative Affective Scale* - PANAS (Watson, Clark, & Tellegen, 1988). Scale translated and adapted to Brazil (Zanon, Bastianello, Pacico, & Hutz, 2013). It is a paper self-report scale, composed by 20 items, that measures positive and negative affect in the past days. It presents a likert scale of 5 points, being 1= not at all and 5= extremely. The scale presents $\alpha = 0.83$ for positive affects and $\alpha = 0.77$ for negative affects. (Appendix D).

- Anxious Thoughts Inventory (Wells, 1994). Scale translated and adapted to Brazil (Moreno et al., 2015). The scale is composed by 22 items that are evaluated through a likert scale of 4 points, being 1= almost never and 4= almost always. This instrument evaluates frequency of anxious thoughts, such as rumination and worry, in the present time. Internal consistency of this instrument is 0.86. (Appendix E).

- Anger Rumination Scale (Sukhodolsky, Golub, & Cromwell, 2001). Scale translated and adapted to Brazil (Sperotto et al., submitted for publication). This instrument consists of 19 items that measure anger rumination over the past six months. It is composed by a 4 points likert scale, being 1= almost never and 4= almost always.

Task and Procedure

The experiment consisted of an adapted Flanker Task, which was originally developed by Eriksen and Eriksen, (1974), to evaluate the effect of noise in an experimental task of inhibitory control. The task was programmed in xml and run in. On each trial of the Flanker task, five horizontally aligned black arrowheads were presented and participants were instructed to respond with the left or right mouse button in accordance with the direction of the central arrowhead. The responses had to be performed with the right hand. The task consisted of 420 trials, divided in seven blocks of 60 trials, with one minute interval between blocks. Participants sat at a viewing distance of approximately 70cm from a 19 inch computer monitor. Set up included one personal computer and a split screen for presenting stimuli. All participants received written instructions on the computer, and were instructed to respond as

fast and as accurate as possible. The trials were randomized and comprised the four congruent X incongruent possibilities (all arrowheads to the right; all arrowheads to the left; distracting arrowheads to the right and central one to the left; and distracting arrowheads to the left and central one to the right). Each set of arrowheads were presented for 200ms, followed by a randomized intertrial interval (ITI) varying from 600ms to 1000ms, presented as a blank screen. The total duration of a trial was approximately 1 second, and the whole task had 14 min duration, approximately. Accuracy and reaction-time for all participants were computed (Appendix F presents the screens of a trial).

To evaluate the effect of performance-worrying and error-monitoring, a procedure to induce worry was introduced. This procedure consisted of providing feedback about the participant's performance by the end of each block. Feedback was programmed in advance on the computer and was not related to the individual's actual performance, but was designed in order to increase worry and irritability. Feedback was displayed on the screen during the one minute interval. On the first, second and third blocks, feedback was neutral and uninformative of the subject's performance (i.e. "okay until this point"). On the fourth, fifth and sixth blocks, feedback was negative and increasingly aversive (i.e. "your performance is very bad, try to be more accurate"). This procedure has been constantly replied in literature (Hajcak et al., 2006, 2012; Holroyd et al., 2006) and presents effectiveness in eliciating higher amplitudes of ERN, calling the individual's attention to the error and being related to RDoC dimensions of performance monitoring and sustained threat. This task is considered particularly relevant in the case of measuring irritability, due to the difficulties of irritable individuals in tolerating frustration. In their studies with anxious and depressive individuals, Hajcak and colleagues (2012) found longer reaction time after the display of the negative feedback, but intact accuracy. Since irritability is a part of the negative affect system, as depression and anxiety, it was expected that the same pattern was found.

Data were collected at Hospital de Clínicas de Porto Alegre, in a room especially designed for EEG experiments. Participants that agreed to participate in the study by phone calls scheduled an appoitment with the reseacher and were independently evaluated. Exclusion criteria, such as the presence of head trauma, neurological disease, use of antipsychotic drugs and left-hand dominance were questioned on the phone calls. Participants that met criteria for the study and accepted to participate were, then, seen by the researcher.

Firstly, all participants received and signed the ethical consent. Secondly, participants were instructed about the EEG procedures and an EEG preparation phase was initiated. That phase was performed by the researcher and a research assistant and had a total duration of

approximately 20 minutes. Once prepared, participants were instructed about the task and began the experiment.

By the end of the experiment, participants were asked to complete the self-report questionnaires, phase that had a total duration of approximately 20 minutes. After completion of the scales, participants were then asked to participate on a diagnostic interview with M.I.N.I. (Sheehan et al., 2002). Diagnostic interviews were performed by the researcher. In case of meeting criteria for any psychiatric disorder, participants were notified and questioned about the need of referral to health centres. Once the interview was completed, participants were accompanied to leave the hospital. Total duration of the procedures was approximately one hour and a half (Appendix G presents a flowchart of the procedures).

Psychophysiological recording, data reduction and analysis

EEG was recorded from 32 Ag/AgCl scalp electrodes embedded in a Mitsar EEG 202 system and referenced to linked mastoids. Midline electrode locations were Fz, Fcz, Cz, Cpz, Pz, Fpz and Oz, and left and right hemisphere sites were Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1, O2, Ft7, Ft8, Fc3, Fc4, Tp7, Tp8, Cp3 and Cp4. Reference electrodes A1 and A2 were located on left and right mastoids, respectively. Signals were amplified with a bandwidth of 0.1 to 30 Hz using a 32-channel Mitsar 202 EEG system running EEGSTUDIO 1.14 (Mitsar, Saint Petersburg, Russia), acquiring EEG data at a 500 Hz sampling rate. Electrode scalp impedances were kept below 5 kΩ. Acquired data were analysed using EEGLAB (Delorme and Makeig, 2004) and ERPLAB (Lopez-Calderon and Luck, 2014), two open source toolboxes for EEG and ERP analysis in MATLAB (MathWorks, Inc, Natick, MA). The continuous EEG data were filtered digitally with a high-pass of 0.1 Hz and a low-pass of 35 Hz. Artifacts were removed using ERPLAB's Moving window Peak-to-Peak algorithm. ERPs were quantified at electrode FCz where error-related brain activity was maximal. Continuous data were separated into epochs ranging from -200 to 1000 ms locked to response onset.

RESULTS

Results of self-report questionnaires and electrophysiological data are presented below. All analyses were conducted with SPSS version 22 and JASP version 0.8.0.1 statistical softwares.

Self-Report Questionnaires

Participants were classified as presenting high angry rumination, high anxious thoughts and high negative affect based on the mean of the total scores of the Anger Rumination Scale, of the Anxious Thoughts Inventory and of the Positive and Negative Affect Scale – Negative Items, respectively. Participants that scored higher than the mean on the scale were then classified as presenting a hight trait of the symptom measured by the scale. The means of the scores of the three questionnaires are presented in Table 3. Participant's identification numbers and scores on each self-report questionnaire is presented in Table 4.

Table 3. Mean and stardard deviation of the scales

	Anger Rumination Scale TOTAL	Anxious Thoughts Inventory TOTAL	PANAS Negative Items TOTAL
Mean	35.9000	41.4000	19.9000
N	10	10	10
SD	14.37938	12.01111	9.13418

Table 4. Participant's id X total scores on self-report questionnaires

Participants id	Score ARS	Score ATI	Score PANAS Neg
02	52	49	34
06	23	28	10
37	30	50	21
52	23	30	20
61	28	43	23
62	31	29	10
63	36	43	18
65	69	67	36
66	29	40	14
67	38	35	13

Label: ARI= Anger Rumination Scale; ATI= Anxious Thoughts Inventory.

According to each participant's results and the mean score of the questionnaires, participants 02, 63, 65 and 67 were classified as presenting high angry rumination; participants 02, 37, 61, 63 and 65 were classified as presenting high anxious thoughts; and participants 02, 37, 52, 61 and 65 were classified as presenting high negative affect.

Due to the overlap in symptoms among participants that scored high in more than one questionnaire, a bayesian correlation analysis was conducted to measure correlation between scales and is presented in Table 5. A bayesian analysis was considered more appropriate

considering the small sample, since it provides a clearer estimate of the amount of evidence present in the data (Jarosz & Wiley, 2014). The hypothesis tested was that the correlation was positive.

Table 5. Bayesian Pearson Correlation for self-report questionnaires

		r	BF_{+0}
ARSTOTAL	- ATITOTAL	0.826	32.92
ARSTOTAL	- PANASNEG	0.787	18.40
ATITOTAL	- PANASNEG	0.848	49.19

Note . For all tests, the alternative hypothesis specifies that the correlation is positive.

In all pairs, Pearson's r is higher than 0.78, indicating a strong correlation between questionnaires. Bayes Factor, on the other hand, is also supporting a positive correlation, as it indicates the number of times the alternative hypothesis predicts data better than the null hypothesis. Figures 1, 1.1 and 1.2 present Bayes Factor Robustness Check for all pairs.
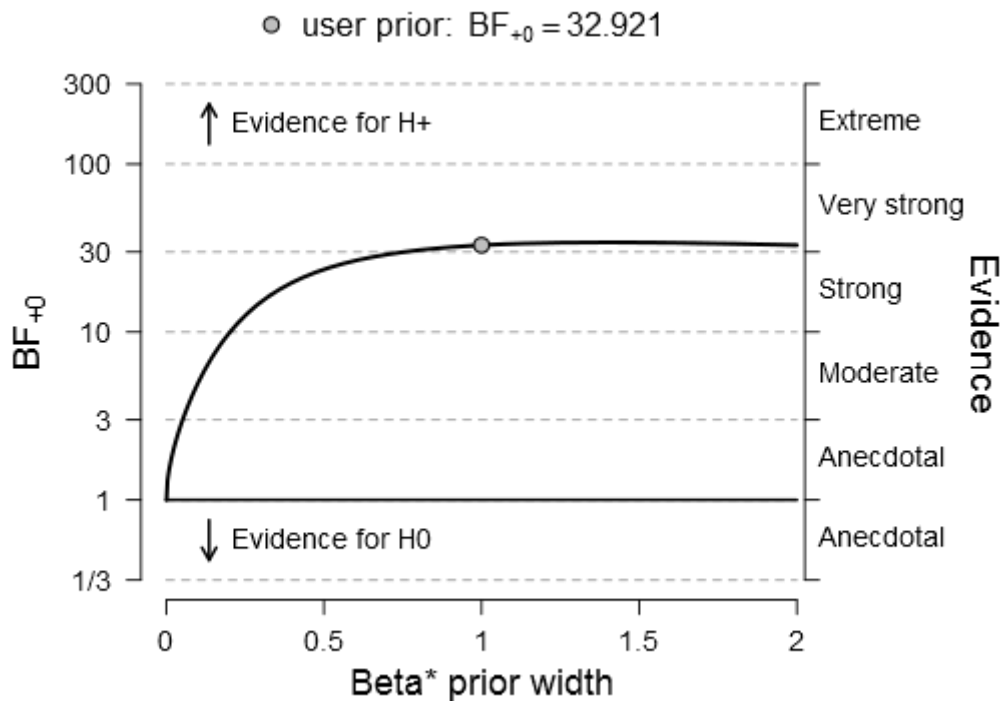
Figure 1. Bayes Factor Robustness Check ARS x ATI

Figure 1.1. Bayes Factor Robustness Check ARS x PANAS Negative
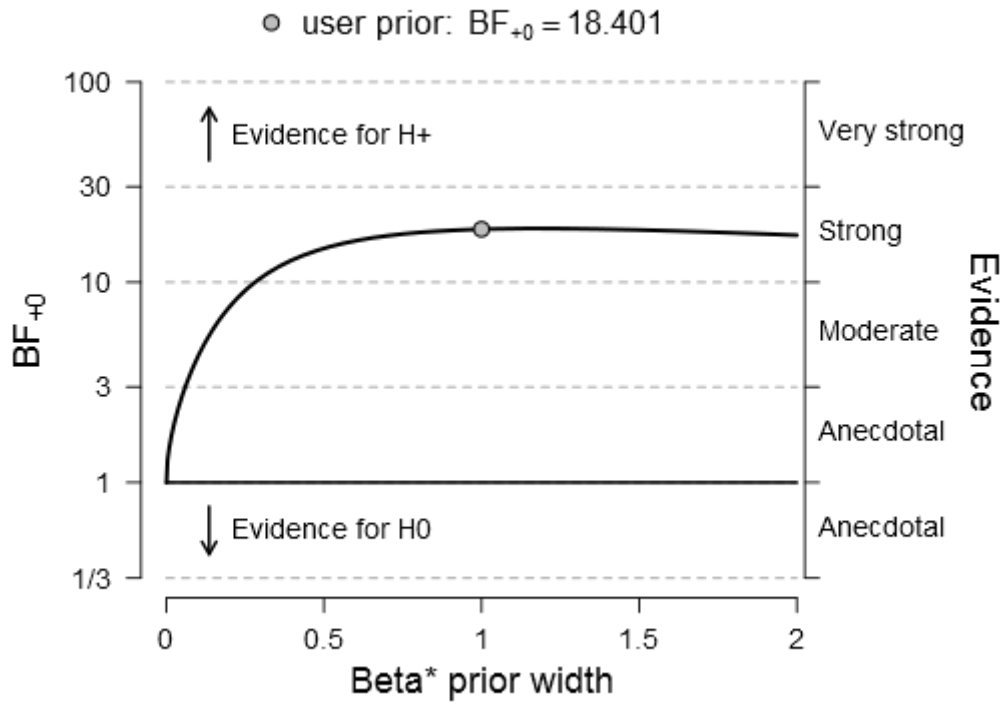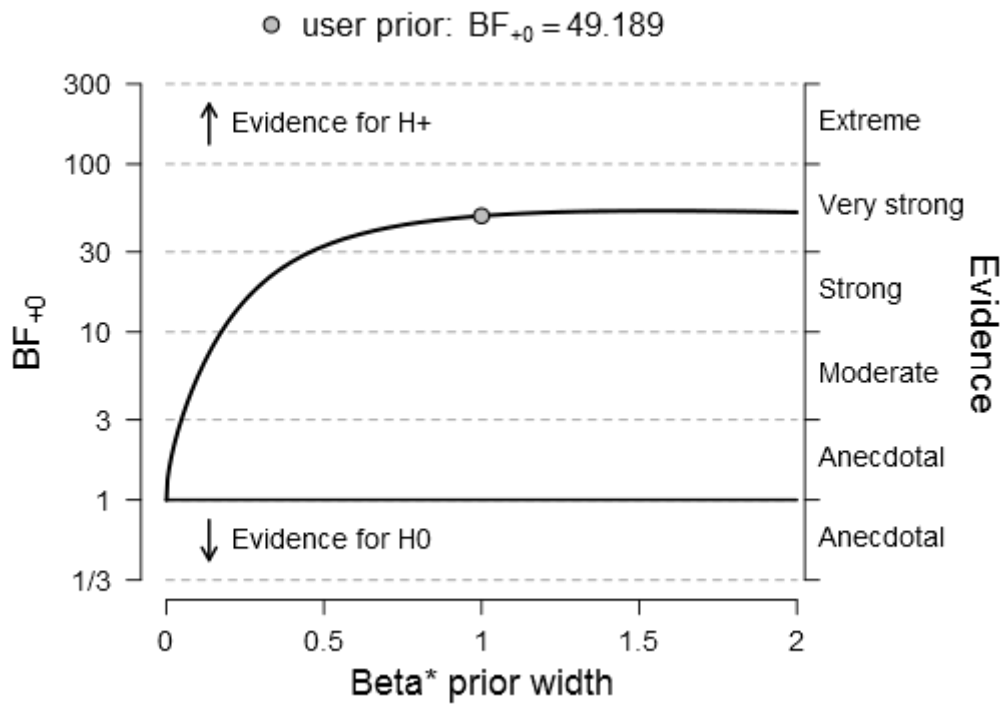

Figure 1.2. Bayes Factor Robustness Check ATI x PANAS Negative

Behavioral results

Number of errors in the task and reaction time values are presented in Table 6. Behavioral data are divided in two phases: Phase 1 = blocks 2, 3 and 4, and Phase 2 = blocks 5, 6 and 7 (post introduction of negative feedback). Block 1 was excluded from analyses and considered as practice phase.

Table 6. Behavioral data

Participant's id	Errors phase 1	Errors phase 2	Mean RT phase 1 (ms)	Mean RT phase 2 (ms)	Mean RT Total (ms)
02	17	11	809.56	792.87	849.81
06	22	13	716.19	720.25	777.85
37	4	8	833.40	887.44	931.93
52	11	35	839.91	749.22	852.77
61	11	21	1053.76	783.30	891.13
62	0	9	922.12	685.05	865.04
63	12	24	739.45	689.23	741.63
65	8	28	636.15	608.04	673.70
66	8	15	660.14	641.15	670.89
67	0	5	869.28	759.54	814.48

Label: RT = Reaction Time

Participant 67 was excluded from EEG analyses due to the commission of fewer than six errors (Olvet & Hajcak, 2009).

ERP results

Figure 2 presents the response-locked ERP waveforms for correct and error responses on FCz. Consistent with previous studies, the ERN was observed as a sharp frontocentral negative deflection that peaked shortly after the commission of an error. The difference between negativity following an error and positivity following a correct answer was statistically significant, as measured by an ANOVA ($F(1.16)=6.6$, $p<0.05$). ERN was less enhanced in phase 2, comparing to phase 1. The difference, however, was not significant ($F(1.16)=0.236$, $p=0.633$), as shown in Figure 2.1. ΔERN was also not statistically significant for phases 1 and 2 ($F(1.16)=2.678$, $p=0.121$).
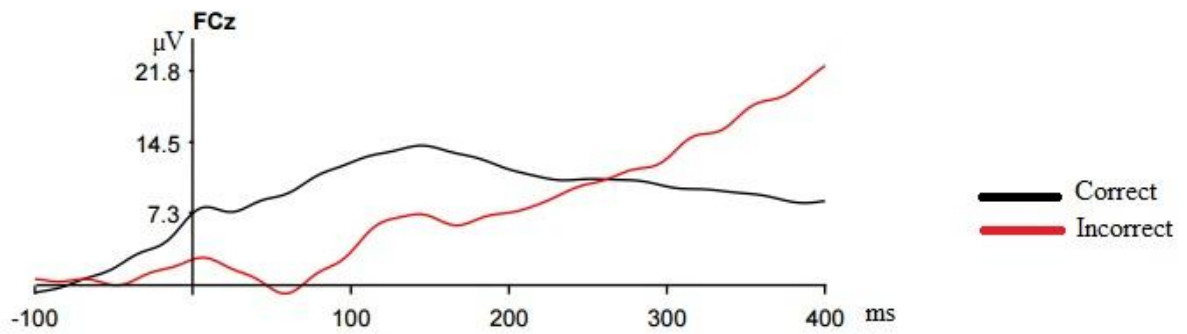
Figure 2. Correct X incorrect trials

Figure 2.1. Incorrect trials phase 1 X incorrect trials phase 2
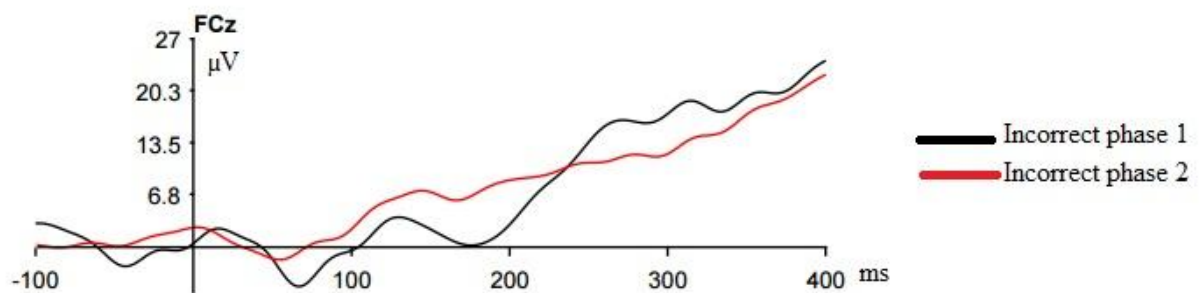
DISCUSSION

In the present paper we have examined performance monitoring in individuals from a community sample, with angry rumination, negative affect and anxious thoughts traits. We aimed to test whether the presence of one of those symptoms/traits, combined to negative feedback in a Flanker task would elicit enhanced amplitudes of ERN, increase the number of errors and enlarge reaction times post-feedback, as seen in the literature of anxious individuals and negative affect (Hajcak, 2012; Moser, 2013; Riesel, 2017).

Interestingly, the comparison between phases 1 (blocks 2,3,4) and phase 2 (blocks 5,6,7, after the introduction of negative feedback) contradicted our hypothesis of enhanced amplitudes of ERN (i.e. more negativity) and longer reaction-times (post-error slowing) in phase 2. We could only replicate the finding of increase of number of errors after negative feedback, with subjects commiting approximately 50% more errors in phase 2, comparing to phase 1.

Humans often require feedback to adapt behavior and perform appropriately. Negative feedback is associated with bad and not expected outcomes, especially when a reward is

expected (Hajcak et al, 2006), and has been largely used in experiments of monetary gain and loss, to verify motivational approach and reward learning (Foti & Hajcak, 2009; Holroyd et al., 2006). In these experiments, subjects are instructed to respond as fast and as accurate as possible and are aware of the possibility to reach good and bad outcomes. Feedback is provided trial-to-trial, providing information about the subject's performance and allowing individuals time to readapt. In our experiment, feedback was only provided at the end of a 60 trial block and referred to the entire block. It is possible that it did not elicit enhanced ERN due to this generalization, since subjects are capable of monitoring correct and incorrect trials without feedback, and negative feedback was provided in all cases, even when subjects were performing above average. We hypothesize that individuals might have disregard feedback and, since it was provided for one minute, might have had time to adapt behavior and continue the task, without presenting post-error slowing and enhanced ERN, as expected (Hajcak, 2012).

Negative affect, especially anxiety, have been exhaustively studied for performance monitoring, and show a pattern of enhanced ERN in basal state and post-feedback (Moser et al., 2013). Inducing negative affect and negative state has also been studied, but its relationship with enhanced ERN remains unclear. To answer this question, Clayson et al. (2012) divided subjects in two groups that performed a Flanker task. One group received positive and the other received derogatory feedback. Their findings showed that there was no difference between groups for reaction-time or ERN amplitudes, suggesting that a state of negative affect is not related to enhanced ERN. On the contrary, ERN seems to be more related to traits than states, indicating its suitability as an endophenotype (Kappenman & Luck, 2016; Olvet & Hajcak, 2008).

It is also possible that an enlarged ERN in phase 2 was not found, due to the characteristics of the sample, that was community and not clinical. Healthy subjects present ERN waves after the commission of errors, however, it is not enhanced as on clinical subjects and remain stable across time (Moser et al., 2013). Also, negative feedback tends to enhance ERN when subjects are expecting outcomes (i.e. monetary gain) or are being evaluated by their performance. In our study, there was no positive or negative outcome expected, thus, it is possible that the reward-learning, cognitive control and sustained threat domains were not activated (Weinberg et al., 2016).

The diminish of reaction-time can be explained in terms of habituation and facility of the task and fatigue. It is possible that reaction-times were longer in phase 1 due to the

novelty of the task, and subjects were requiring more time to process information. In block 4, after 180 trials, subjects might have gotten habituated to the task and start answering faster.

Another possibility is that the subjects started presenting fatigue, since the task was long and repetitive. The lack of positive outcomes and rewards might have been responsible for the non-activation of the reward learning system (Weinberg et al., 2016), and subjects did not engage in the task. Studies suggest that ERN might reflect error-detection that is utilized for motivational ends (Olvet & Hajcak, 2008).

Fatigue might also explain why errors increased in phase 2, since subject's attention could be impaired by the length of the task (Boksem et al., 2005). Another possibility is that subjects were bored, due to a repetitive task, and have disengaged attention (Eastwood et al., 2012). A third option is that the negative feedback produced anxiety on subjects, culminating in more impulsive and incorrect answers. Several studies have demonstrated the effects of worry on cognitive performance and the difficulties of anxious individuals to disengage attention from threatening stimui (Hajcak et al., 2003; Moser et al., 2013; Weinberg et al., 2015; Zambrano-Vazquez & Allen, 2014).

Anxious individuals tend to respond faster and might present slightly decreased accuracy, compared to healthy individuals (Hajcak et al., 2003; Riesel et al., 2016), which could explain why individuals in phase 2 presented faster reaction time and increase of the number of errors. Negative feedback, in this case, could be eliciting the sustained threat domain, capturing individuals' attention to constant threat (Weinberg et al., 2016). It is still unclear, though, if individuals with irritability, also part of the negative affect systems, as anxiety, present the same pattern.

To our knowledge, this is the first study that has evaluated the relationship between performance monitoring and irritability, thus, much remains unclear about the direction of ERN and irritability disorders. Several components and variables might be mediating the results found, as negative affect, worry, rumination, motivation and attention. Since our subjects were not clinical, it is difficult to predict which findings are caused by symptoms' traits and which are related to individual differences. Our subjects presented highly heterogeneous profiles, making it difficult to translate the findings. It is essencial, then, to conduct more studies, in order to elucidate the relationship between error-related negativity and irritability disorders.

FURTHER CONSIDERATIONS

The heterogeneity of mental disorders represents difficulties for research, since an unlimited number of variables might be responsible for human behavior and feelings. Due to these challenges, research focusing on neuroscience tools and techniques are essencial to minimize diagnostic errors and to elucidate mechanisms underlying mental disorders (Insel et al., 2010).

Endophenotypes, unobservable characteristics that mediate the relationship between genes and a given behavioral phenotype (Olvet & Hajcak, 2008), are important tools as biomarkers and can help assisting premature diagnosis and posterior more effective treatment (Sanislow et al., 2010). Endophenotypes, however, are characteristics associated to diseases, thus, for its research, it is important to submit subjects with similar symptoms to the same task, in order to find differences.

Our study, though, presents limitations. First, the heterogeneity between individuals' symptoms (different traits and different intensity) difficults the finding for endophenotypes, since they are related to trait and not state symptoms (Olvet & Hajcak, 2008). Second, the feedback provided might not have been ideal, due to the limited number of times it was presented and since it was not related to a positive or negative outcome, making it less likely for subjects to engage in the task (Hajcak et al., 2006; Holroyd et al., 2006). Trial-to-trial feedback is considered more appropriate for these studies, for they assist behavior regulation and individual's adaptation to the task. Error-related negativity seems to be associated to motivational systems, and our paradigm without rewarding might have affected the amplitude of ERN. Third, the small sample size might have affected our results. Most studies evaluate at least 30 individuals to find significant and reliable results. Nevertheless, we have found significant results for ERN on overall incorrect X correct trials, indicating that the task was appropriate to elicit ERN and supporting literature for the inclusion of ERN as an unit of analysys on RDoC's sub domain "performance monitoring".

The evaluation of irritability traits in adults is challenging, since there are no diagnoses of irritability for this population. Future studies should, then, conduct experiments on the relationship between irritability symptoms in a more homogeneous population, induce irritability on a trial-to-trial negative feedback basis and enlarge the sample size, in order to elucidate the direction of performance monitoring in irritability and its pattern as part of the negative affect systems.

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APPENDIX

34

HOSPITAL DE CLÍNICAS DE PORTO ALEGRE - HCPA / UFRGS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Estudo de Negatividade Relacionada a Erro (ERN) como Biomarcador do Monitoramento de Erro em Adultos com Alta Irritabilidade

Pesquisador: Gustavo Gauer

Área Temática:

Versão: 2

CAAE: 56362716.4.0000.5327

Instituição Proponente: Hospital de Clínicas de Porto Alegre

Patrocinador Principal: CONS NAC DE DESENVOLVIMENTO CIENTIFICO E TECNOLOGICO

DADOS DO PARECER

Número do Parecer: 1.627.656

HOSPITAL DE CLÍNICAS DE PORTO ALEGRE - HCPA / UFRGS

Continuação do Parecer: 1.627.656

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 06 de Julho de 2016

Assinado por:
José Roberto Goldim
(Coordenador)

APPENDIX B – Informed Consent

Título do Projeto:

Estudo de negatividade relacionada a erro (ERN) como biomarcador de traços de irritabilidade em adultos saudáveis: uma perspectiva RDoC

Você está sendo convidado a participar de uma pesquisa cujo objetivo é avaliar sintomas de irritabilidade, através de questionários e de ondas cerebrais. Esta pesquisa está sendo realizada pelo Instituto de Psicologia da Universidade Federal do Rio Grande do Sul e pelo Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA).

Se você aceitar participar da pesquisa, os procedimentos envolvidos em sua participação são os seguintes:

1) Você responderá a questionários que avaliam a forma como você se sente, como pensa e a presença de sintomas ansiosos e depressivos. Alguns desses questionários serão autoaplicáveis (você mesmo preenche) e outros serão realizados por entrevistas com uma psicóloga. Essa etapa durará em torno de uma hora e meia.

2) Após os questionários, você fará uma tarefa em frente a um computador na qual você seguirá comandos no teclado solicitados por um programa de computador. Durante a tarefa no computador, a sua atividade cerebral será registrada por sensores (eletrodos) colocados com uma touca no couro cabeludo, na face (testa) e orelhas. Além disso, é colocado um cinto na altura do peito para manter a touca firme. Nenhum desses instrumentos emite qualquer sensação como choque ou calor. A tarefa terá duração de vinte minutos e a colocação dos eletrodos com a touca em torno de 30 minutos.

Após a etapa 1, você será comunicado se foi identificado algum sintoma de irritabilidade ou qualquer outra condição que necessite de acompanhamento médico ou psicológico. Neste caso, a equipe de pesquisa fará o encaminhamento necessário.

Os possíveis desconfortos decorrentes da participação na pesquisa são a possibilidade de você se sentir incomodado em responder as perguntas do questionário, pois algumas perguntas são referentes à sua vida particular. Se você se sentir desconfortável, você poderá solicitar ao pesquisador a interrupção em qualquer momento, e caso necessite de algum atendimento especializado, comunique ao pesquisador que ele realizará o encaminhamento adequado. Ainda, você pode se sentir cansado ao responder as perguntas e executar a tarefa. Caso isto aconteça, você pode comunicar ao pesquisador, que imediatamente lhe atenderá no sentido de contornar a situação.

Os possíveis benefícios decorrentes da participação na pesquisa são ajudar, de maneira pessoal, a reconhecer algum problema existente do qual você não tinha conhecimento. Poderá também ajudar profissionais da área da saúde a avaliar corretamente um paciente com irritabilidade, o que influencia em seu tratamento e na sua melhora do transtorno.

Sua participação na pesquisa é totalmente voluntária, ou seja, não é obrigatória. Caso você decida não participar, ou ainda, desistir de participar e retirar seu consentimento, não haverá nenhum prejuízo ao atendimento que você recebe ou possa vir a receber na instituição.

Não está previsto nenhum tipo de pagamento pela sua participação na pesquisa e você não terá nenhum custo com respeito aos procedimentos envolvidos.

Caso ocorra alguma intercorrência ou dano, resultante de sua participação na pesquisa, você receberá todo o atendimento necessário, sem nenhum custo pessoal.

Os dados coletados durante a pesquisa serão sempre tratados confidencialmente. Os resultados serão apresentados de forma conjunta, sem a identificação dos participantes, ou seja, o seu nome não aparecerá na publicação dos resultados.

Caso você tenha dúvidas, poderá entrar em contato com o pesquisador responsável, Dr. Gustavo Gauer, pelo telefone (51) 3308 5303, com a pesquisadora Ana Maria F.L. Pereira de Souza, pelo telefone (51) 3308 5303 ou com o Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre (HCPA), pelo telefone (51) 3359 7640, ou no 2º andar do HCPA, sala 2227, de segunda à sexta, das 8h às 17h.

Esse Termo é assinado em duas vias, sendo uma para o participante e outra para os pesquisadores.

_____   _____

Nome do participante da pesquisa   Assinatura

_____   _____

Nome do pesquisador que aplicou o Termo   Assinatura

Porto   Alegre,   de   de   2016

APPENDIX C- Socio-Demographic and General Health Questionnaire

A partir de agora você irá responder a um questionário sócio-demográfico e de saúde geral.

Q1 Sexo:

- o Feminino
- o Masculino

Q2 Idade: _____

Q3 Lateralidade manual:

- o Destro
- o Canhoto
- o Ambidestro

Q4 Você possui problemas visuais não corrigidos?

- o Sim
- o Não

Q5 Você sofre de daltonismo?

- o Sim
- o Não

Q6 Raça:

- o Caucasiano(a)
- o Negro(a)
- o Amarelo(a)
- o Pardo(a)
- o Outro _____

Q7 Estado civil:

- o Solteiro(a)
- o Casado(a)
- o Separado(a)
- o Divorciado(a)
- o Viúvo(a)
- o União estável
- o Outro _____

Q8 Nível de instrução:

- o Ensino fundamental incompleto
- o Ensino fundamental completo
- o Ensino médio incompleto

- o Ensino médio completo
- o Ensino superior incompleto
- o Ensino superior completo
- o Pós-graduação lato senso incompleta
- o Pós-graduação lato senso completa
- o Mestrado incompleto
- o Mestrado completo
- o Doutorado incompleto
- o Doutorado completo
- o Pós-doutorado incompleto
- o Pós-doutorado completo

Q9 O que você cursa ou cursou na pós-graduação? _____

Q10 Curso de graduação:

_____

Q11 Situação ocupacional:

- o Estudante
- o Estudante (bolsista)
- o Profissional liberal
- o Empregado com carteira assinada
- o Empregado sem carteira assinada
- o Funcionário público
- o Autônomo
- o Do lar
- o Sem atividade remunerada
- o Outro _____

Q12 Nacionalidade:

- o Brasileira
- o Outra _____

Q13 Em que cidade você nasceu? _____

Q14 UF: _____

Q15 Em que cidade você residiu maior parte da sua vida? _____

Q16 Onde você mora?

Rua: _____ Nº:_____
Complemento:_____ CEP:_____ Bairro: _____ Cidade:
_____ UF:_____

Q17 Renda individual: _____

Q18 Renda familiar: _____

Q19 Quantas pessoas vivem dessa renda? _____

Q20 Religião: _____

Q21 Pratica essa religião?

- o Sim
- o Não

Q22 Usa alguma medicação atualmente, incluindo psicofármacos?

      Q23 Qual(is)? _____

      Q24 Dose(s)? _____

      Q25 Há quanto tempo? _____

Q26 Já realizou ou realiza algum tipo de tratamento psiquiátrico ou psicológico?

- o Sim, realizo.
- o Sim, realizei.
- o Não.

      Q27 Qual(is)? _____

Q28 Fumante?

- o Sim
- o Não
- o Fumo raramente
- o Outro _____

Q29 Você ingere bebidas alcoólicas com que frequência?

- o Não bebo.
- o Uma ou duas vezes ao ano.
- o Uma ou duas vezes a cada seis meses.
- o Uma ou duas vezes a cada três meses.
- o Uma ou duas vezes por mês.
- o Uma vez por semana.
- o Duas vezes por semana.
- o Três vezes por semana.
- o Quatro ou cinco vezes por semana.
- o Diariamente.
- o Outro _____

Q30 Nos últimos 12 meses, em três ou mais ocasiões você bebeu pelo menos cinco latas de cerveja ou uma garrafa de vinho ou três doses de uma bebida alcoólica forte (pinga, caipirinha, conhaque, vodca, uísque...), num período de três horas?

- o Sim
- o Não

Q31 Quanto à sua ingestão de álcool:

Você já pensou em largar a bebida?	Sim	Não
Ficou aborrecido quando outras pessoas criticaram seu hábito de beber?	Sim	Não
Se sentiu mal ou culpado pelo fato de beber?	Sim	Não
Bebeu pela manhã para ficar mais calmo ou se livrar de uma ressaca (abrir os olhos)?	Sim	Não

Q32 Você ingeriu álcool ou consumiu alguma outra droga hoje?

- o Sim
- o Não

    Q33 A que horas, o que e qual a quantidade?

    _____

    _____

    _

Q34 Hoje em dia você faz uso de alguma droga, mesmo que ocasionalmente?

- o Sim
- o Não

Q35 Qual(is)?

Q36 Quantidade:

Q37 Periodicidade:

- o Diariamente
- o De 4 a 6 dias por semana
- o De 2 a 3 dias por semana

- o 1 vez por semana
- o 2 ou 3 vezes ao mês
- o 1 vez ao mês
- o 1 vez a cada 3 meses
- o 1 vez a cada 6 meses
- o 1 vez ao ano
- o Outro _____

Q38 Você usou drogas no passado?

- o Sim
- o Não

Q39 Qual(is)? _____

Q40 Quantidade:

Q41 Periodicidade:

- o Diariamente
- o De 4 a 6 dias por semana
- o De 2 a 3 dias por semana
- o 1 vez por semana
- o 2 ou 3 vezes ao mês
- o 1 vez ao mês
- o 1 vez a cada 3 meses
- o 1 vez a cada 6 meses
- o 1 vez ao ano
- o Outro _____

Q42 Você ingeriu alguma bebida à base de cafeína hoje?

- o Sim
- o Não

Q43 Se sim:

Q44 Quantidade? _____

Q45 Há quanto tempo? _____

Q46 Há quanto tempo você se alimentou pela última vez? _____

Q47 Você está se sentindo cansado ou com sono agora?

- o Sim
- o Não

Q48 Você possui algum transtorno neurológico?

- o Não.
- o Não sei, mas acho que não.
- o Não sei, mas acho que sim.
- o Sim.
- o Outro _____

Q49 Qual(is)? _____

Q50 Atualmente, você sofre de algum transtorno psiquiátrico?

- o Não
- o Suspeito que sim.
- o Sim.
- o Outro _____

Q51 Qual(is)? _____

Q52 Você toma alguma medicação ou realiza algum tipo de terapia/tratamento para isso?

- o Sim, estou medicado.
- o Sim, faço terapia.
- o Sim, estou medicado e faço terapia.
- o Não.

Q53 Se você tiver interesse em realizar algum tipo de tratamento para seu transtorno, por favor, deixe seu e-mail que lhe indicaremos locais que prestam serviços de saúde.

_____

Muito obrigada por participar da nossa pesquisa!

Escala de Afetos Positivos e Negativos (PANAS)

Esta escala consiste em um número de palavras que descrevem diferentes sentimentos e emoções. Leia cada item e depois marque a resposta adequada no espaço ao lado da palavra. Indique até que ponto você tem se sentido dessa forma ultimamente.

1	2	3	4	5
Nem um pouco	Um pouco	Moderadamente	Bastante	Extremamente

1. Aflito
2. Amável
3. Amedrontado
4. Angustiado
5. Animado
6. Apaixonado
7. Determinado
8. Dinâmico
9. Entusiasmado
10. Forte
11. Humilhado
12. Incomodado
13. Inquieto
14. Inspirado
15. Irritado
16. Nervoso
17. Orgulhoso
18. Perturbado
19. Rancoroso
20. Vigoroso

*Os itens 1,3,4,11,12,13,15,16,18,19 referem-se a afetos negativos e os itens 2,5,6,7,8,9,10,14,17,20 referem-se a afetos positivos.

APPENDIX E – Anxious Thoughts Inventory – ATI

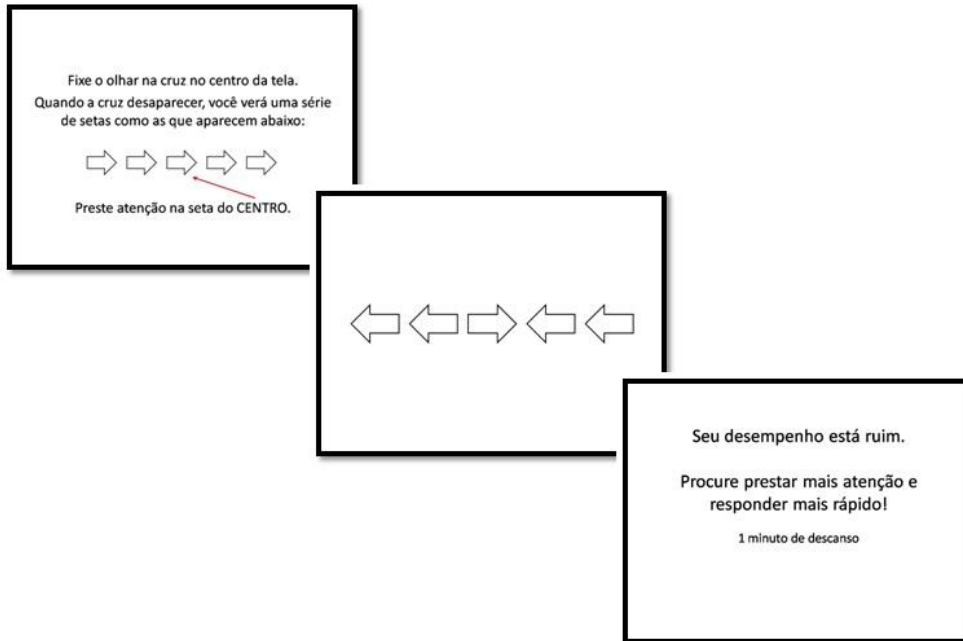|		Quase Nunca	Às vezes	Frequent emente	Quase Sempre
1.	Eu me preocupo com minha aparência.	1	2	3	4
2.	Eu acho que sou um fracasso.	1	2	3	4
3.	Quando olho para o meu futuro, penso mais sobre coisas negativas que podem me acontecer do que coisas positivas.	1	2	3	4
4.	Se eu tenho sintomas físicos inesperados, tenho a tendência de pensar que a pior coisa possível está acontecendo comigo.	1	2	3	4
5.	Eu tenho pensamentos com a possibilidade de ficar seriamente doente.	1	2	3	4
6.	Eu tenho dificuldade de limpar minha mente de pensamentos repetitivos.	1	2	3	4
7.	Eu me preocupo com a possibilidade de ter um ataque cardíaco ou câncer.	1	2	3	4
8.	Eu me preocupo se vou dizer ou fazer algo errado no meio de estranhos.	1	2	3	4

9.	Eu me preocupo sobre minhas capacidades não corresponderem às expectativas dos outros.	1	2	3	4
10.	Eu me preocupo com minha saúde física.	1	2	3	4
11.	Eu me preocupo por não conseguir controlar meus pensamentos tão bem quanto eu gostaria.	1	2	3	4
12.	Eu me preocupo com as pessoas gostarem de mim.	1	2	3	4
13.	Eu levo as decepções tão a sério que não consigo tirá-las da minha cabeça.	1	2	3	4
14.	Eu fico constrangido facilmente.	1	2	3	4
15.	Quando eu tenho problemas simples de saúde, como uma mancha na pele, eu penso que eles são mais graves do que realmente são.	1	2	3	4
16.	Pensamentos desagradáveis entram na minha cabeça contra minha vontade.	1	2	3	4
17.	Eu me preocupo com meus fracassos e minhas fraquezas.	1	2	3	4
18.	Eu me preocupo em não ser capaz de enfrentar a vida tão bem quanto os outros parecem conseguir.	1	2	3	4
19.	Eu me preocupo com a morte.	1	2	3	4

20.	Eu me preocupo com a possibilidade de parecer idiota na frente dos outros.	1	2	3	4
21.	Eu acho que estou perdendo coisas na vida por me preocupar demais.	1	2	3	4
22.	Eu tenho pensamentos repetitivos, como ficar contando ou repetindo frases.	1	2	3	4

## APPENDIX F- Example of the screens of a Trial

This appendix illustrates the sequence of the screens in one trial. In this example, the trial was incongruent.

The screens will be presented separately, to provide a better visualization.

Fixe o olhar na cruz no centro da tela.
Quando a cruz desaparecer, você verá uma série de setas como as que aparecem abaixo:

Preste atenção na seta do CENTRO.

Seu desempenho está ruim.

Procure prestar mais atenção e responder mais rápido!
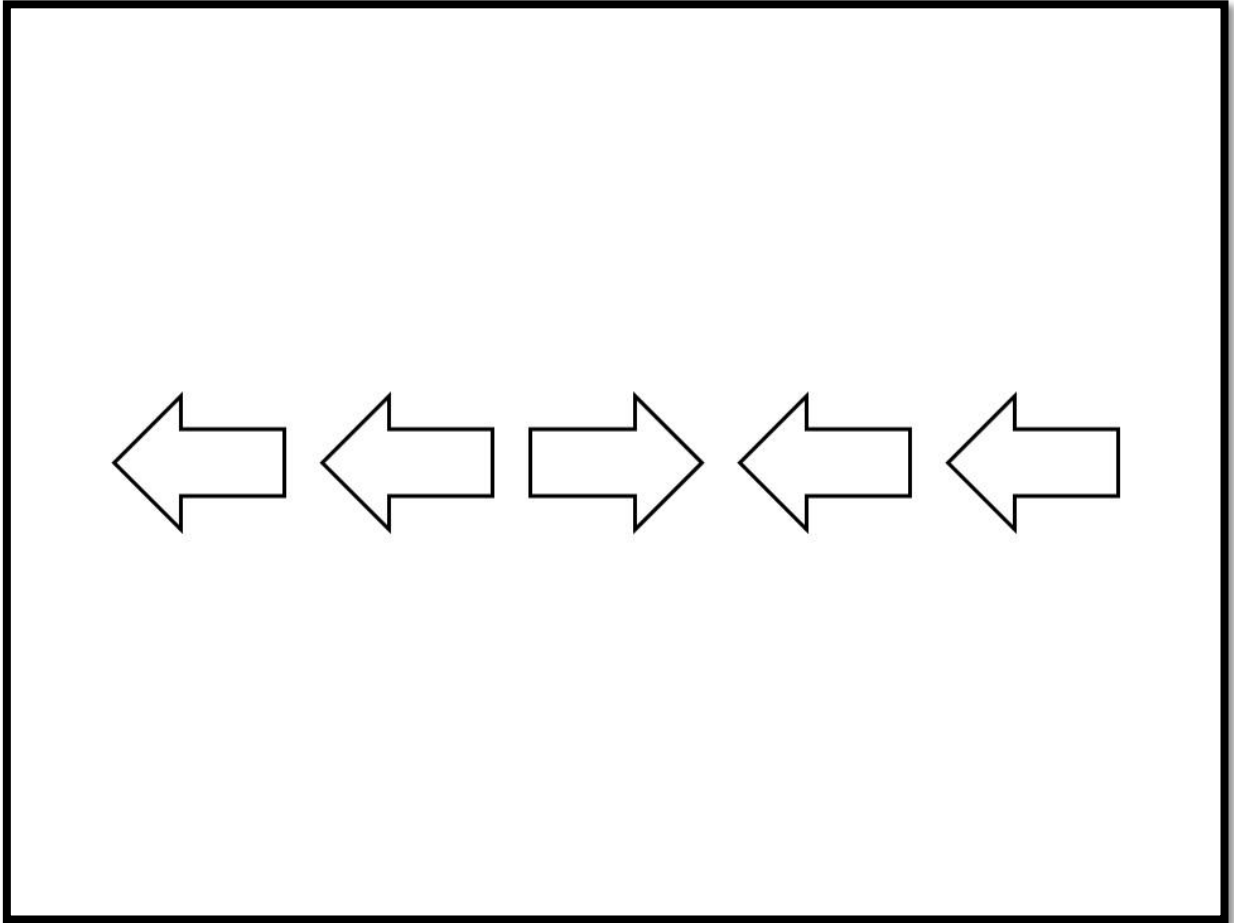
1 minuto de descanso

Screen 1 – Instructions

Fixe o olhar na cruz no centro da tela.

Quando a cruz desaparecer, você verá uma série de setas como as que aparecem abaixo:
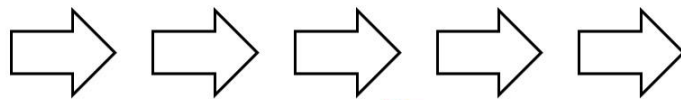
Preste atenção na seta do CENTRO.

Screen 2 – Stimuli

Presented for 200 ms.

Screen 3 – Feedback

Seu desempenho está ruim.

Procure prestar mais atenção e
responder mais rápido!

1 minuto de descanso

Presented only at the end of a block, for one minute.

APPENDIX G – Flowchart of the procedures

This appendix presents the sequency of the main moments of the research.

Informed Consent

EEG preparation

EEG experiment

Socio-Demographic and General Health Questionnaire

Anxious Thoughts Inventory

Positive and Negative Affective Scale

Anger Rumination Scale

M.I.N.I.