UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE PSICOLOGÍA

TESIS DOCTORAL

Disfunción de la Corteza Temporo-Parietal y el Circuito de la Atención como Endofenotipo de la Depresión

Temporo-Parietal Cortex and Attention Circuit Dysfunction as Endophenotype of Depression

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Javier de Echegaray y Díaz de Otazu

Director

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Madrid

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Intoducción

La depresión supone uno de los problemas de salud mental de mayor incidencia en la población, generando grandes costes económicos, sociales y humanos para la sociedad, además de presentar una alta comorbilidad con otros desórdenes emocionales y una elevada tasa de mortalidad (Paykel et al., 2005). La naturaleza familiar del trastorno depresivo mayor ha sido confirmada a través de diversos estudios y se ha planteado como un trastorno parcialmente causado por componentes genéticos (Gershon, 1982; Odgerel et al., 2013; Sullivan et al., 2000) y sus interacciones con las condiciones ambientales (Disner et al., 2011; HEATH et al., 1999; Vázquez C. et al., 2010). Por ello, se ha considerado que personas con historia familiar de depresión tienen mayor posibilidad de presentar endofenotipos depresivos (Odgerel et al., 2013).

En general, el trastorno depresivo mayor (en adelante MDD) es tratado como un desorden afectivo caracterizado por un procesamiento alterado de la información emocional. Por ello, las anormalidades en el funcionamiento cerebral subyacentes a estos procesos y asociadas a la historial familiar de MDD deberían ser buenos candidatos para la identificación de endofenotipos de depresión.

Existe una acumulación de medidas electrofisiológicas de la asimetría cerebral en los circuitos atencionales en el procesamiento emocional que podría evidenciar la expresión de tales endofenotipos, en la que los pacientes con depresión exhiben asimetrías en actividad alfa EEG en electrodos posteriores y déficits conductuales que apuntan a una disfunción temporo-parietal derecha (Blackhart et al., 2006; Bruder et al., 2002) La asimetría de potencia alfa en regiones posteriores del hemisferio derecho parece estar bajo influencia genética, así como la hipo actividad cortical posterior derecha, dependiendo de la carga familiar de depresión (Bruder et al., 2002; Kayser et al., 2017) habiendo sido observada en individuos con carga familiar de depresión, independientemente de que sufrieran o no depresión, reforzando la hipótesis de la

presencia de un endofenotipo de depresión ubicado en regiones corticales posteriores (Odgerel et al., 2013).

Se ha comprobado que la oscilación posterior de las respuestas neuromagnética y electrofisiológica ante imágenes emocionales registradas mediante Magnetoencefalografía (MEG) o Electroencefalografía (EEG) están moduladas por el arousal emocional (Bradley, 2009; Moratti et al., 2004, 2008, 2015) : los estímulos con altos niveles de arousal emocional concuerdan con estructuras corticales relevantes a la atención como la corteza parietal derecha (Moratti et al., 2004, 2008, 2011)), apuntando que el arousal dirige los circuitos relevantes para la atención, facilitando así el procesamiento atencional de estímulos emocionalmente relevantes (Vuilleumier, 2005; Vuilleumier & Driver, 2007). Mientras la actividad cortical temporo-parietal derecha se encuentra modulada por el arousal emocional en sujetos controles sanos, pacientes con depresión muestran una ausencia acusada de este efecto modulatorio (Deldin, Keller, Gergen & Miller, 2000; Kayser, Bruder, Tenke, Stewart & Quitkin, 2000; Moratti et al., 2008). Estos descubrimientos indican una deficiente coordinación de los circuitos cerebrales relevantes para la atención en la modulación de arousal emocional en la depresión.

A pesar de ello, actualmente no se conoce si la reducción de modulación de arousal en las redes corticales atencionales observada en pacientes con MDD descansa sobre su carácter hereditario o no. Más aún, no hay estudios hasta la fecha que relacionen estas disfunciones corticales específicas con la regulación emocional en sujetos sanos y en pacientes con trastorno depresivo mayor con y sin antecedentes familiares de depresión.

Objetivos

(1) Estudiar la respuesta de pacientes con MDD y sujetos controles sanos con y sin historia familiar de depresión en regiones corticales relevantes en el procesamiento atencional mediante el registro de actividad biomagnética cerebral (Magnetoencefalografía), durante la visualización de estímulos emocionales bajo un paradigma *steady-state Visual Evoked Fields* (ssVEF). (2) Analizar estas diferencias a nivel periférico mediante el análisis de la respuesta cardiaca (Electrocardiograma) y (3) la eventual relación entre ambas respuestas. (4) Explorar las eventuales diferencias a nivel volumétrico (Resonancia Magnética Estructural) de la amígdala en relación tanto a la depresión como a los antecedentes familiares de sintomatología depresiva, y su relación con la respuesta cortical.

Resultados

A nivel cortical, el análisis de la interacción entre los factores de historia familiar de depresión (FH) y el estatus de depresión (MDD), revelaron diferencias significativas en regiones fronto-parietales derechas, en las que los sujetos control con historia familiar de depresión mostraron una mayor amplitud de la respuesta ssVEF en la corteza parietal derecha y frontal izquierda en comparación con aquellos controles sin FH. Esta tendencia mostro un patrón opuesto en la corteza frontal derecha, en la que los controles con FH mostraron una reducción de la amplitud ssVEF en comparación con los controles sin FH. Por otro lado, no se encontraron diferencias significativas con respecto a la FH entre los pacientes con MDD. El análisis entre el grupo control y los pacientes con MDD reveló una reducción de la amplitud de la respuesta ssVEF en pacientes con MDD en regiones fronto-parietales derechas, reflejando una respuesta atencional atenuada en comparación con el grupo control.

El análisis de la respuesta cardiaca reveló una respuesta cardíaca atenuada de los pacientes con depresión ante imágenes de contenido emocional negativo entre los 2 y los 6 segundos de exposición, mientras que no se encontraron diferencias en función de la presencia de FH, ni en la interacción entre ambos factores.

La relación entre la respuesta cortical y cardiaca reveló una fuerte correlación entre la desaceleración cardiaca y la actividad de la corteza parietal, poniendo de manifiesto el carácter atencional de la respuesta de orientación, donde no se encontraron diferencias significativas en función de la MDD ni de la FH.

Por último, a nivel volumétrico encontramos un incremento significativo del volumen de la amígdala en los pacientes con MDD. Más aun, la correlación entre el volumen de la amígdala y las puntuaciones obtenidas en el cuestionario HDRS para depresión, reveló una fuerte correlación entre el volumen de la amígdala y la severidad de la sintomatología depresiva. Además, las diferencias entre el grupo control y MDD en la respuesta ssVEF, se vieron incrementadas cuando se introdujo el volumen de la amígdala como covariable en el análisis, poniendo de manifiesto el rol de la amígdala en la respuesta atencional a imágenes emocionalmente relevantes. A pesar de ello, no encontramos diferencias significativas en el volumen de la amígdala con respecto a la FH ni a la interacción entre ambos factores.

Conclusiones

A pesar de que la premisa principal de esta tesis era la caracterización de la corteza temporo-parietal derecha como endofenotipo de la depresión, los resultados obtenidos revelan una naturaleza más compleja en le interacción MDD-FH, en la que los resultados sugieren una desregulación en el funcionamiento de la red fronto-parietal derecha ante estímulos emocionalmente relevantes.

Por otro lado, comprobamos que la respuesta de pacientes con MDD en comparación con sujetos controles sanos, exhibe un patrón de respuesta atenuada tanto a nivel del sistema nervioso central (ssVEF) como autónomo (tasa cardiaca).

Nuestros resultados sugieren que las diferencias en la regulación emocional se ven influidas sobre todo por los estímulos negativos de alto arousal, confirmando la relevancia de la modulación de arousal emocional en el procesamiento atencional en la MDD.

Por último, nuestros resultados ponen de manifiesto la importancia de la amígdala en la MDD como centro clave en el procesamiento emocional, además del rol crucial de ésta en la respuesta atencional ante estímulos emocionalmente relevantes.

Abstract

Introduction

Depression is one of the most prevalent mental disorder which generates great social, economic and human costs. Beyond, it presents a high comorbidity with other affective disorders and a high mortality rate (Paykel, Brugha & Fryeres, 2005). The familiar nature of the major depressive disorder (onwards, MDD) has been highlighted by several studies, and therefore, MDD has been conceptualized as a disorder originated by genetic components (Gershon et al., 1982; Sullivan, Neale & Kendler, 2000; Talati, Weissman & Hamilton, 2013) and its interaction with environmental factors (Bierut et al., 1999, Vázquez C. et al., 2010, Disner et al-. 2011). Therefore, individuals with a family history of depression (onwards, FH) are considered to manifest more likely depressive endophenotypes (Tatali et al., 2013).

In general, MDD is considered as an affective disorder characterized by an altered emotional processing. Therefore, the abnormalities in the brain functioning underlying these processes associated to the FH status should represent reliable candidates for endophenotypes of depression.

The electrophysiological evidences of brain asymmetries within the attentional circuits involved in the emotional processing could evidence those endophenotypes, where MDD patients exhibit alpha-band asymmetries in EEG posterior electrodes linked to behavioral deficits pointing to the dysfunction of the right temporo-parietal cortex in MDD (Blackhart, Minnix & Kline, 2006; Bruder et al., 1997; Bruder, Wexler, Stewart, Price & Quitkin, 1999; Henriques & Davidson, 1990; Jaeger, Borod & Peselow, 1987; Kentgen et al., 2000; Kucharska-Pietura & Davi, 2003). Previous evidence has related the alpha asymmetry in right posterior regions to genetic factors, as well as the hypo-activation of the right posterior cortex to the familial load of depression, observed in depressed and non-depressed individuals with and without FH (Bruder et al., 2005; Bruder et al., 2007),

emphasizing the temporo-parietal hypothesis of the MDD endophenotype (Talati et al., 2013).

The posterior EEG and MEG oscillations to emotional images have been shown to be modulated by emotional arousal (Keil et al., 2003; Keil, Moratti, Sabatinelli, Bradley & Lang, 2005: Moratti, Keil & Stolarova, 2004; Moratti, Rubio, Campo, Keil & Ortiz, 2008): highly-arousing stimuli agree with relevant attentional processing structures activation, such as the right parietal cortex (Moratti et al., 2004; Moratti et al., 2008; Moratti, Saugar & Strange, 2011), pointing to the role of arousal for attentional circuits, and facilitating hence the attentional processing of emotionally relevant stimuli (Vuilleumier, 2005; Vuilleumier & Driver, 2007). While the right temporo-parietal activity is modulated by emotional arousal in healthy subjects, MDD patients show a lack of arousal modulation in this region (Deldin, Keller, Gergen & Miller, 2000; Kayser, Bruder, Tenke, Stewart & Quitkin, 2000; Moratti et al., 2008). Taken together, these findings point to the deficient coordination within the attentional circuitry of the emotional arousal modulation in MDD.

However, it still unknown whether the reduced arousal modulation in the attentional circuit relies or not on genetic factors involved in MDD. Further, to the date, there are not studies relating cortical arousal modulation dysfunction in healthy individuals and MDD patients with and without family history of depression.

Objectives

(1) Evaluating the neuromagnetic (Magnetoencephalogram) cortical response of healthy subjects and MDD patients with and without FH of depression in attentional relevant regions during the viewing of highly arousing emotional pictures using a *steady-state Visual Evoked Fields* (ssVEF) paradigm. (2) Evaluating autonomous nervous system responses by a cardiac response analysis (Electrocardiogram) (3) and characterizing the relationship between both psychophysiological responses. (4) To explore the volumetric differences (Magnetic Resonance Imaging) of the amygdala

regarding MDD and the FH status of depression and its relationship with the cortical response in attentional brain circuits.

Results

At the cortical level, the analysis of the interaction of MDD and FH factors revealed significant differences within the healthy group in right fronto-parietal regions, while no significant difference emerged within the MDD group. Healthy controls with FH exhibited greater ssVEF amplitudes in the right parietal and the left frontal cortices compared to healthy subjects without FH. On the other hand, the right frontal cortex showed the opposite tendency, where healthy controls with FH exhibited a reduced ssVEF amplitude when compared to healthy subjects without FH.

The contrast between healthy controls and MDD patients revealed a reduced ssVEF amplitude at right fronto-parietal regions in MDD patients compared to healthy controls, reflecting the attenuated response in attentional brain regions of MDD patients compared to the control group.

The analysis of the cardiac activity revealed a general blunted heart rate change response of MDD patients to emotional pictures, which was significantly different to the control group between the 2nd and the 6th seconds of unpleasant pictures presentation. No significant difference emerged in the cardiac activity regarding the FH factor, nor the interaction between both factors.

The relationship between cardiac and cortical responses revealed a strong correlation between the cardiac deceleration and the enhanced ssVEF amplitude of the parietal cortex, emphasizing the attentional character of the orienting response, where no differences were found regarding the MDD, the FH and the interaction between both factors.

Finally, the volumetric analysis of the amygdala revealed an increased volume of the amygdala of MDD patients compared to healthy controls. Moreover, correlation analysis revealed a strong correlation between the amygdala volume and the severity of MDD

symptoms estimated by HDRS scores. Beyond, the differences between both groups with respect to emotional ssVEF modulations were greater when the amygdala volume were introduced in the contrast analysis as a covariate. However, no significant differences were found regarding the FH and the interaction between both factors.

Conclusions

Although the main hypothesis of the study focused on the temporoparietal cortex as an endophenotype of the depression, the results depict a more complex nature with respect to the interaction between MDD and FH. Here, the results suggest an impaired processing in attentional brain regions within right fronto-parietal network when viewing highly arousing emotional pictures. 00

Additionally, the current findings demonstrate an attenuated response pattern of MDD patients compared to healthy individuals to highly arousing unpleasant pictures with respect to both, central and peripheric levels, as indicated by a blunted cardiac response and reduced ssVEF amplitude modulation in right fronto-parietal regions.

Finally, the results highlight the relevant role of the amygdala in the MDD and its crucial role in the attentional processing of highly relevant emotional pictures.

1 Brief review of emotions across history

Emotions have been considered a cornerstone of modern psychology. However, this consideration is not new. Attending to the etymological origin of the word itself, emotion results from the Latin word *emotio*, *emotionis* derived from the verb *emovere*, which results from the verb movere (to move) and the prefix e-/ex- (from), meaning to move or to evict from a site. According to this definition, emotion would be an event that moves someone from his habitual place. Likewise, we find several words derived from the Latin verb *movere*, such as motion, motor, or mobile. The general concept behind all of them would be the act of moving. Therefore, emotion could be understood as the ultimate reason to generate movement.

Western civilization has focused on emotion as an essential element of human behavior during the last decades, but again, this study is not new. To find the first theory of emotions enounced in western thinking, we must travel (of course) to ancient Greece. Plato introduced the primary division of the soul in three main domains: cognitive, affective, and appetitive domain, which correspond to reason, appetite, and spirit. Plato crystallizes this trilogy of the soul, analyzing the role of intelligence by the opposition of pain and pleasure. The psychological correlates of these domains would correspond to cognition, motivation, and emotion, where cognition would represent the rational component in charge of driving affective and appetite aspects of emotion and motivation.

On the other hand, Aristotle dedicates part of the second book "Ars Retorica" to the study of passions and character, where he claims that emotion is the result of every soul affection accompanied by pleasure or pain. Thereby, Aristotle considered the emotions as reactions of a being to an auspicious or hostile position. As opposed to Platoon, Aristotle considered that emotions would be composed of rational and irrational elements simultaneously (Aristotle, 1997).

In front of this functional perspective the stoicism conceptualized emotions as a chronic illness that could be globalized in four primary emotions: on the one hand, happiness for the

present pleasure and longing of future pleasure, and in opposition, affliction for the present damages and fear for the future ills. Under this logic, emotions supposed to be meaningless wrong reality judgments and had no function at all. That is why wise men stay above them using reason to keep themselves from this affection.

This dichotomic conception of emotions would correlate to a posterior way of thinking in classical Rome, where philosophy was imbued in the stoicism stream. This way, Cicero maintains that happiness (great soul) is only reachable by the practice of virtue and the use of reason, subordinating emotions and passions to reason and moral thinking, knowing that instinct tends to pleasant emotions. In front of this, Epicurus defends the search for pleasure itself at the same time that locates the good itself in a middle point of pleasure and pain.

Seneca, which begins from the stoicism guidelines, introduces a physiological component of emotions (passions) that cannot be controlled. On the other hand, he tried to focus on the cognitive component of emotions, which can be dominated by a regulated regimen of food and drink and music. Here we see how Seneca dissociates physiological reactions and proposes music as a therapeutic method to control emotions. (Lucio Anneco Séneca, 41 C.E.)

This way of thinking that locates the reason in the middle of the self and considers it the only way to control emotions will leave its mark on the Christian considerations about emotion. Saint Thomas Aquinas categorizes emotions as the appetitive component of the soul, controllable by the human will, which corresponds to the apprehensive component of the soul (Santo Tomás de Aquino, 1225). In opposition to this peripatetically perspective, Juan Huarte de San Juan defends the existence of a physiological organ, which would have the role of the understanding, previously attributed to a non-physical soul (Juan Huarte, 1603).

The functional consideration of emotions continues since these considerations. Authors such as Hobbes or Telesio recognize the biological function of pleasure or pain. Hobbes conceptualized emotions as one of the four human faculties with the physical stretch,

the experience, and the reason. He considered emotions as the invisible principle of the movement of the human body (Thomas Hobbes, 1651). He also introduces different categories for different emotions, including the absence of it: contempt, which is defined as immobility. This approach includes the notion of emotions as motors for human will and behavior.

One step further from Hobbes's idea of emotions as invisible motors, Hume (1751) introduces the idea of emotion as measurable processes such as any physic phenomena. For him, emotions are also affected by the interaction of preexistent ideas and thoughts, adding a cognitive level plus the physiological substrate of emotions (David Hume, 1751).

Aligned to this initial physiological perspective of emotions, Descartes (1649) considered the Pineal gland as the joint of soul and body. Under his dualistic perspective of emotions, he considered this brain region as the place where emotions reside (Descartes R., 1649). He also introduced the idea that every emotion would be composed of six primitive emotions (love, hate, happiness, sadness, astonishment, and desire). Including the astonishment as a fundamental emotion, Descartes opposes the traditional dichotomic perspective, as long as it cannot be classified as positive/negative, nor pleasure/pain.

This dualistic perspective of body/soul will be refuted by Spinoza (1670), for whom emotions involve both as different elements of the same reality (Spinoza B., 1970). Consistent with stoicism, he differed in the functional perspective of emotions, pointing out emotions as confusing thoughts (Leibniz, 1734). As we will see, this controversy will still patent the psychophysiological study of emotions until the XX century.

Attending to this perspective, Kant introduces the prior universal perceptions of human beings: space and time, based on which humans perceive and experience the environment (Kant, 1781). Likewise, he first dissociated the concept of feeling as an independent category between will and reason and recognized a moral component of emotions. Despite his stoicism conception of feelings, he stills defends the biological function of emotions and the necessity to overcome these to dominate the inner soul.

Following the concept of feeling, Hegel (1807) raises the distinction between feeling, emotion, and passion, considering feelings as universal categories that can be considered utilitarian depending on the pragmatic objective of the specific feeling (Hegel, 1807).

2 Classic approaches of emotion

Emotion as a psychological concept was first introduced in psychology by William James and Lange in 1884. James described emotion as a set of organic, visceral, and muscular changes in the organism. Under this perspective, emotions would be a side effect induced by the perception of the peripheral changes of the organism and not directly biased by perceptions or thoughts (James, 1884.).

From this physiological perspective of emotions, the emotions would not be the cause but the consequence of organic changes that would define the emotion itself. In other words, James would defend that individuals are sad because they cry and not the other way around. Therefore, each emotion would be defined by a specific pattern of physiological changes.

Despite this emergent physiological approach, this perspective of emotions has been controversial from its birth. One of the foremost critics of this model came from Cannon, who claimed that emotions trigger the organic response (Cannon, 1915). One of the main arguments against the James-Lange approach was that the same set of autonomic changes of an emotional reaction could be elicited by drugs administration but without emotional conscience. Cannon also adds a primary role to the central nervous system instead of focusing only on the visceral reaction as the leading actor, as James did previously. Cannon's model (1915) also proposes a whole nervous system reaction where the perceptual stimulation is processed by the thalamus and analyzed across the cortex. Then the output is sent to the autonomic nervous system, provoking the emotional expression and the emotional experience. For Cannon, the emotional expression would have an adaptative function where the emotion would prepare the organism for a fight or flight response. Under this view, there would be no specific visceral reaction for each emotion, while the differences across emotional reactions would be quantitative.

Nonetheless, the study of the emotional dimension of human beings has not been univocal. Two main approaches crystalized: the discrete approach and the dimensional approach.

2.1 Discrete approach

Originating from the previously described James-Lange emotional theories, the discrete approach claims the discrete character of emotions, being these isolated and mutually exclusive ones within themselves. This approach assumes the hierarchical existence of two main categories of emotions: basic and secondary emotions.

2.1.1 Basic Emotions

This model defends that each emotion is defined by its own set of physiological changes, which are different from the rest of them. This particular set of characteristics for each emotion would be represented by specific facial expressions and physiological responses controlled by specific anatomical and functional neural correlates.

Under the discrete approach, the basic emotions would be the result of an evolutionary process, and therefore, the resulting emotions would have an adaptive character for the individual. Under the evolutionary perspective, the basic emotions also have an innate character and therefore are universal and shared for all human beings.

One of the prominent defenders of this adaptive model and responsible for the characterization of the basic emotions was the American psychologist Paul Ekman (1934), who determined that the basic emotions were composed of: fear, anger, happiness, sadness, disgust, and surprise (Ekman, Levenson & Ellsworth, 1983). During the ’80s, some authors added two more basic emotions to this set of six: anticipation and acceptance (Plutchik, 1984)

1. To prove the universal character of the basic emotions, Ekman and Friesen, developed several studies under a facial expression paradigm. Individuals from different cultures in different world regions were asked to pair emotional faces with basic emotional

labels (Ekman et al., 1969). These studies found a high correlation between specific facial expressions and the previously mentioned basic emotions, pointing out then supporting the universal character of basic emotions.

2. There are also studies based on emotional facial recognition developed not only across cultures but across ages: under the evolutionary perspective, basic emotions are conceptualized as innate. Therefore, several studies focused on emotional facial recognition in infants between three and nine months old to test the inherent condition of basic emotions, finding that during this life period, infants were able to recognize the specific facial patterns (Iglesias et al., 1989).

3. The other central postulate of basic emotions references those to specific functional and structural neural correlates. Due to Ekman's contributions, the studies of the specific responses for basic emotions became a subject of interest during the second half of the XX century. Its psychophysiological aspects were tested under several paradigms to test differences in visceral activity in response to different emotions. The main paradigms of these studies are based on the elicitation of emotional states, where individuals are exposed to emotional stimuli (usually emotional complex scenes and emotional faces) and the stimulation of facial muscles like corrugators. At the same time, autonomic supervision (such as blood current, cardiac response, skin conductance, pupil diameter size, or intestinal motility) was monitored (Ekman et al., 1983). Despite their efforts, there is still no clear evidence of the existence of a particular set of physiological responses for each particular emotion (Carretié et al., 2001.). The crucial findings, such as differences in the skin conductance while pleasant and unpleasant personal experience revival and the variation of cardiac response while complex emotional scene viewing, cannot explain differences across Ekman's six basic emotions. One of the main arguments exhibited by Ekman to explain the lack of evidence for the specific physiological response would be the limitation of the methodological approaches. In addition, the limitations of resolution in physiological measurements would make no possible to find significant differences across conditions (Cacioppo et al., 1994).

On the other hand, according to Lang's model of defense cascade, individuals can exhibit different responses to the same emotions depending on environmental circumstances, like the relative distance to the object (Lang, Bradley & Cuthbert, 1997).

Taken together, it is still unclear the existence of a specific autonomic pattern response for each basic emotion that proves the specific underlying functional and structural neural network for each basic emotion.

2.1.2 Secondary Emotions

The discrete approach comprises a set of secondary emotions which would result from the combination of the basic ones (McDougall, 1926). The main difference between basic and secondary emotions resides in the social component of the secondary ones; this way, emotions like remorse would be composed of sadness and disgust and would strongly influence the social environment (Robert Plutchik, 1984). Under this perspective, remorse would be different under the catholic perspective than under the deterministic approach, the same way that love would be conceptualized differently during the high middle ages than during romanticism. Plutchik (1984) also introduces three main characteristics of discrete emotions; under his consideration, emotions are discrete but quantitative due to varying intensity. Emotions also can be more or less similar between them; this way, love would be more related to optimism and less to deception. Finally, emotions are polarized: love would be the opposite of hate, the same way optimism would be the opposite of deception. Taking these three precepts of emotions and the eight basic emotions proposed by him, Putchik develops a structural-psychoevolutionary model of emotion where each emotion would result from the dimensional combination of other emotions (Robert Plutchik, 1984). Other authors base the characterization of the secondary emotions on the specific neuroanatomical paths for each emotion (Izard., 1971; Izard, 1977). However, this characterization has also been one of the most controversial points in the criticism of this model due to the lack of consensus on the evidence of specific neuroanatomical paths for each secondary emotion (Ortony & Turner, 1990). Another main critique of the discrete model derived from the secondary emotions is the lack of consensus in its categorization; while authors like Izard

narrow down a set of 10 different secondary emotions, Ekman defends only six basic emotions, which is due to the different categorization system used by the different authors which would redound in a lack of consistency of this model.

In summary, it is worth mentioning that this model defends the primacy of emotions over cognition and the functional character of emotions: making possible communication across individuals and increasing their chances of survival.

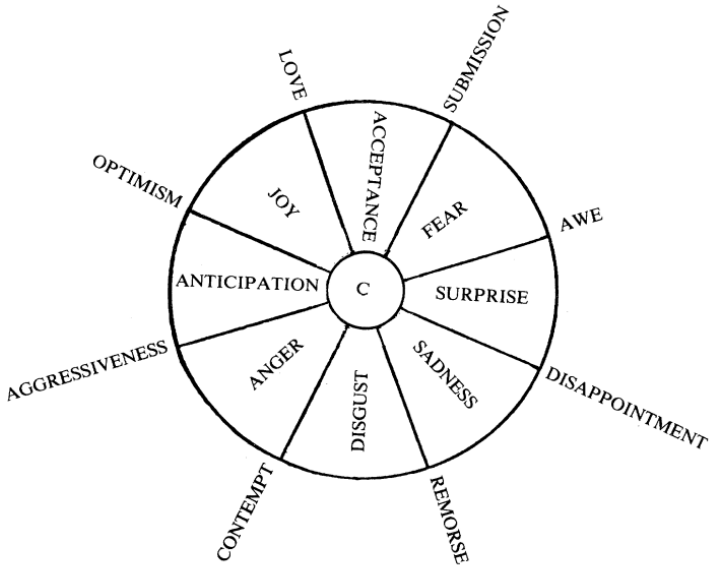


Figure 1.1. Spatial graphic representation of the basic and the secondary emotions proposed by the disc approach. Taken from Putchik 1984.

2.2 Dimensional approach

Opposed to the classical approach of the discrete model of emotions and at odds with it, different authors claim for a dimensional model where emotions are distributed among a continuous space of a particular dimension, defending the ambiguous character of affective experience of emotions. Thereby, individuals do not experiment emotions as isolated or categorical entities (Posner et al., 2005).

The conceptualization of the dimensions have differed across authors: negative-positive affect (Huelsman et al., 1998; Tellegen et al., 1999), tension and energy (Thayer, 1989), approach-avoidance (P. J. Lang et al., 1990; P. J. , Lang et al., 1997), and valence & arousal (J. A. Russell, 1980).

2.2.1 The circumplex Model

One of the most representative models under this paradigm, the circumplex model of affect, introduced by Russell (1980), arises as a response to the categorical approach. Under this perspective, "all affective states arise from cognitive interpretations of core neural sensations that are the product of two independent neurophysiological systems" (Posner et al., 2005). These two independent systems are defined among two continuous dimensions: valence and arousal. While the valence determines the dynamic polarization from pleasant to unpleasant, the arousal dimension defines the potential excitement that a specific emotion evokes in an organism, from relaxing to activating. Under this perspective, emotions are distributed among these two dimensions (Figure 2) (P. J. Lang et al., 1997a) and, therefore, defined by the linear combination of independent dimensions representing a particular emotion that arises from the cognitive interpretation of physiological changes (Posner et al., 2005).

The circumplex model of affect was not only a theoretical approach but the framework for emotional attention studies. Therefore, many experimental studies were developed under this approach using similar scalar ratings for facial emotional expressions (Abelson & Sermat, 1962; Cliff & Young, 1968; J. A. Russell & Bullock, 1985; Schlosberg, 1952) or

emotional relevant words (Bush, 1973; Kring et al., 2003; D. A. Russell et al., 1980). Moreover, the psychophysiological study of emotional attention like skin conductance, heart rate change (Codispoti et al., 2001), facial electromyography measurements of corrugator and (Cacioppo et al., 1986a, 1994; P. J. Lang et al., 1990), functional magnetic resonance imaging (Bradley et al., 2003) or electroencephalography (Keil et al., 2001a) were inspired by this categorization system were the psychophysiological measurements under passive viewing task paradigm of emotional images were related with subjective arousal ratings and valence categorization.

However, despite the independency between arousal and valence assumed by this model, the empirical data reflects the strong relationship between them (see IAPS section below and Figure 3).

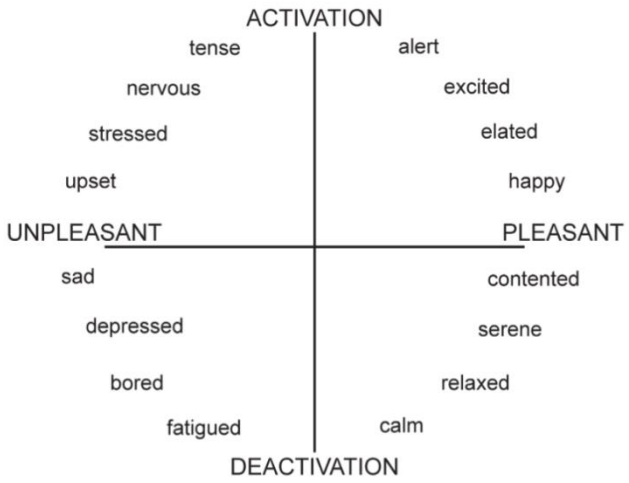


Figure 1.2. Spatial graphic representation of the emotions among the emotional dimensions valence and arousal proposed by the dimensional approach.

2.2.2 The Motivated Attention

From a dimensional approach and the dimensional categorization system, Peter Lang's research group focused on how attention is determined primarily by motivation under natural conditions. Therefore, motivated attention rises from an adaptive evolutionary substratum. This way, emotions would be dispositions for the action of the individual which result in discrete responses to stimuli: from a psychoevolutionary view, the emotions would encourage the organism to an approach/avoidance behavior depending on the appetitive or aversive character of the stimuli, which would redound on higher probabilities of survival (Konorski, 1967). The motivated attention determines that the emotion elicited by the stimuli responds to an internal disposition of the organism to an approach behavior (food or sex), which would redound on increased probabilities of survival. In the same way, the presence of potential danger (snakes or guns) would motivate an avoidance behavior such as the so-called fight-or-flight or the opposed freezing response, resulting in higher probabilities of survival. Under this framework, emotions are an evolutionary response characterized by the preparation of the appropriate response, and therefore, emotions are considered action dispositions (P. J. Lang, 1995). In other words, motivation has a priming effect (potentiation/diminution) on the response of the individual to a particular event (Lang, Bradley, Cuthbert, 1997)

Hence, two different systems modulate emotion and perception: appetitive and aversive motivational systems. Both systems have different psychophysiological paths and structures responsible for the corresponding somatic and autonomic reaction (Bradley, 2009), and the response of these systems are distributed among three different levels: the subjective experience of the individual, the neurophysiological changes induced by the central and autonomous nervous systems' activity and the behavioral (P. J. Lang, 1995). The pattern response at these different levels defines the emotion. However, they do not have to be perfectly correlated with each other (P. J. Lang, 1995).

In the same way as the circumflex model, motivated attention characterizes emotions among the continuous dimensions of valence and arousal to classify them on the appetitive-

aversive continuum. Critically, within the motivated attention approach, arousal cannot be considered independent from valence: while valence indicates to which motivational system (appetitive-aversive) an emotion can be mapped on, the arousal reflects the strength of the activation of the corresponding motivational system (Bradley, 2001; Schupp, et al., 2005).

2.2.2.1 The International Affective Picture System (IAPS)

Considering the evolutionary character of motivated attention, it makes sense that the majority of the population would roughly agree on the classification of emotions. To this end, Lang and his team created the IAPS (P. J. Lang et al., 1997a), which consists of a standardized, well-validated set of photographs that have been pre-rated in terms of valence and arousal implementing the Self-Assessment Manikin (Bradley & Lang, 1994). Contrary to what the circumflex approach considered, they found a C-shape distribution across valence and arousal instead of a uniform distribution of emotions (figure 3).

In order to test the different response systems and SAM classification, they developed a vast pool of images that are distributed around both dimensions and an additional dimension of affective dominance, which relates to the self-perceived control degree of the situation.

Even when the evolutionary character of the model assumes the biological character of the approach-avoidance system, the IAPS takes into account the eventual social differences on the rating scales for each different country taken from the sample of this one (P. J. Lang et al., 1997a). After the standardization stimuli of IAPS, most studies of motivated attention were carried out under visual tasks paradigms.

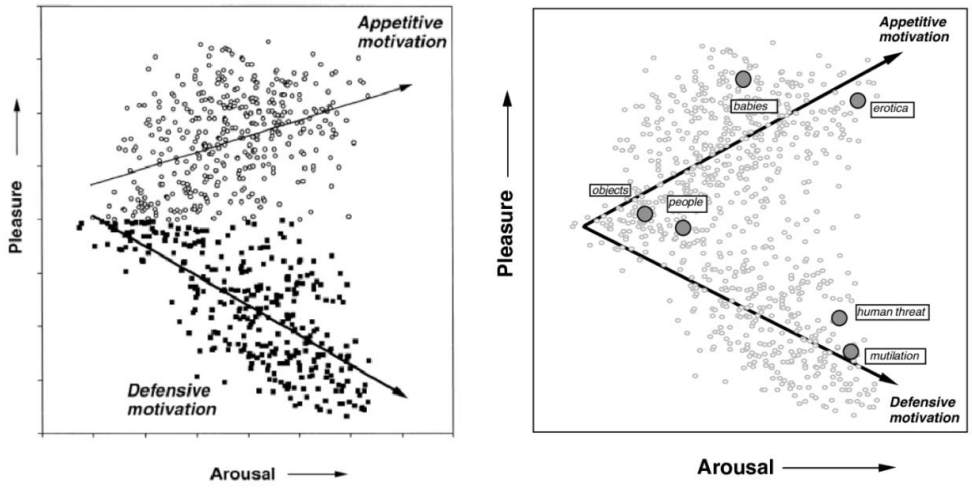


Figure 1.3. Spatial graphic representation of the stimuli distribution among the emotional dimensions valence and arousal of the IAPS (left). The graphic distribution of the six main subcategories chosen for the three main experimental conditions for the present study (neutral: objects & people; pleasant: babies & erotica; unpleasant: attack & mutilation) (Right). Taken from Lang et al., 1997.

2.2.2.2 Appetitive vs. Aversive System

Even when the motivated attention model proposes an appetitive and aversive motivational system, researchers have paid attention predominantly to the aversive one. This is probably due to the methodological implications of eliciting appetitive conditions and higher levels of arousal, redounding on more extreme physiological responses on the individual for either human beings or other animals (Cacioppo et al., 1994; P. J. Lang et al., 1997b). Consistently with the adaptive biological relevance of the stimuli, and to the fact that most of we know about the cortical and subcortical activity comes from animal models with rodents under painfully events and fear-conditioned stimuli. Nevertheless, even when most studies focus on the aversive system, we also have evidence of the appetitive system performance.

As previously mentioned, while the traditional model claims for a unitary psychophysiological system responsible for the valence evaluation of stimuli belonging to a unitary path and wire (Papez circuitry) that respond to any emotional stimuli for any valence, the evidence provided by research under the circumplex frame points to strong evidences in favor of separate system (at least in part) for each valence category (Bradley, 2009; Junghöfer et al., 2005; Schupp et al., 2007). Under this framework, some systems are activated by aversive stimuli, while others are by appetitive ones. An excellent example of this is the role of the amygdala: while the first evidence of amygdala activation defends the indiscriminate role of this one on the emotional processing (J. E. LeDoux, 1995a), later reported results to point to a more excessive activation of the amygdala during aversive stimuli processing (Adolphs, Russell, et al., 1999; J. E. LeDoux, 1995b). However, amygdala activation also occurs during appetitive stimulus processing (Adolphs, Tranel, et al., 1999; Cahill & McGaugh, 1990; Méndez-Bértolo et al., 2016).

Based on animal models, the amygdala is still considered as the core system for the defense response under aversive situations, where the sensory input are relayed directly from thalamic nuclei to the amygdala (first to the lateral and latter to the central nuclei (J. LeDoux et al., 1990)). Depending on the specific defense response, the somatic changes are mediated

through different neural centers: while the autonomic response depends on the lateral hypothalamic path, the somatic components rely on the periaqueductal central gray area. Specifically, the ventral central gray matter would be related to the freezing response, while the dorsal would be responsible for the fight/flight response (see Figure 4) (P. J. Lang et al., 1997).

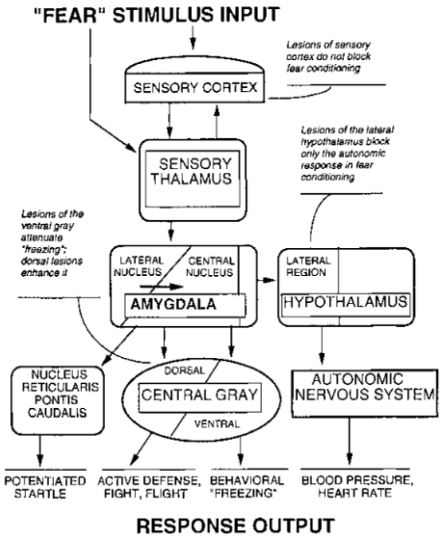


Figure 1.4: schema of nervous circuitry involved in the attentional processing of relevant stimuli proposed by Lang, Bardley and Cuthbert (1997). Taken from Lang et al. (1997).

On the other hand, the research on the appetitive motivational system and approach response point to the mesolimbic system, where the ventral tegmental area projects to the accumbens nucleus, which has a strong connection with the dorsolateral prefrontal cortex, amygdala, and hippocampus (Adolphs, Russell, et al., 1999; Posner et al., 2005). The dopaminergic character of the mesolimbic system has also been studied by stimulating dopamine by drug administration and repetitive electrical self-stimulation in the orbitofrontal cortex and ventral striatum (caudate & accumbens), resulting in reinforced behaviors (see Figure 5).

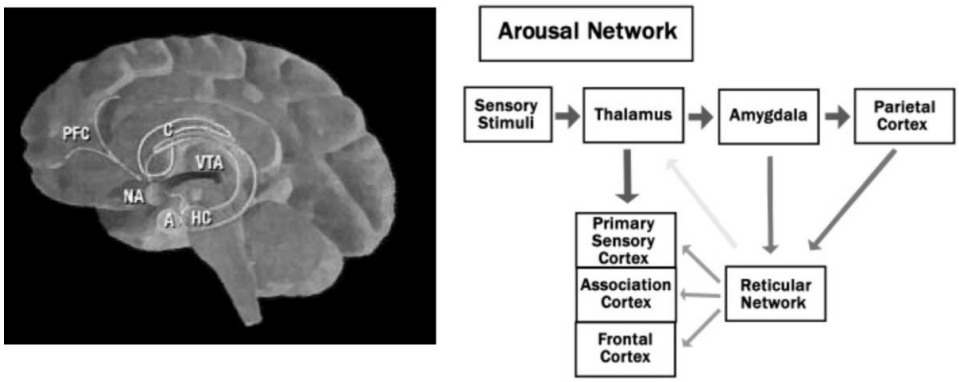


Figure 1.5: illustrates the Arousal network schema of the Papez brain circuitry.

Aside, EEG studies have found congruent cortical activation to subjective ratings on arousal, revealing a similar activation pattern (Keil et al., 2001b), while peripheral measurements of the facial electromyography of the corrugators and zygomatic musculature have been successfully correlated with valence ratings (Bradley et al., 1993; Cacioppo et al., 1986b).

Finally, several studies developed on brain reaction to emotional induction have systematically found differences in the presence of depression compared to healthy

conditions. Further analysis of this evidence will be introduced and discussed in section 1 and section 4 from chapter 2.

3 Major Depressive Disorder

3.1 Brief review of depression across history

Etymologic origin of depression comes from the Indo-European prefix de-, which indicates the top-down direction of something, followed by –press- which evolves from Latin *pressus* (thin, small, profound, or pressure) or *premere* (to press). The final termination *–ion*, also derived from the Indo-European and indicates the action or effect of something. As followed indicated, the psychological definition of depression consistently agrees with the etymologic interpretation of this concept, indicating the effect of depressing or a sunken activity period.

Major depressive disorder has been widely described in the psychological bibliography from both clinical and experimental psychology. However, the symptoms associated with this pathology have been historically described since the beginning of the literature, where depression (as many other psychological syndromes) has been read from demonic possessions in the popular culture and religion to organic infections in nineteen-century clinical medicine. The first evidence of depression as a health disorder comes from the first Babylonian empire (second millennium B.C.), where is written down in a compilation of health illness and is related to terms such as distress, breaking mind, constantly afraid and even a cutting off of (Reynolds & Wilson, 2013).

Hippocrates, for his part, considered the origin of melancholia under its perspective of the unbalance of the humors. Concretely, he attributes the melancholia to greater levels of black bile, which should be treated with bloodlettings, baths, exercise, and diet. Cicero attributed melancholia to a psychological process derived from anger and fear (Tipton, C., 2014).

Nonetheless, it was not until the late nineteenth century when we find a clinical concept of depression as a diagnosed syndrome, where the referred word was melancholia, which, coming from the Greek, refers to the depressed humor of an individual. Melancholia is understood as a unitary syndrome isolated from any other different mental disorder. This kind of perspective comes from the categorical Nosology approach developed by Kraepelin during the late nineteenth century under the framework of Wundt's experimental psychology.

3.2 Current categorization of major depressive disorder

Nowadays, the current conception of the major depressive disorder in psychology and psychiatry is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (latest version DSM-5, 2013) and the International Statistical Classification of Diseases and Related Health Problems (ICD) (latest version ICD-11, 2010). Both manuals try to offer a unified guideline for a unified diagnosis of mental disorders. However, it is worth mentioning that the modern concept of depression itself has also been changing across the periodical revisions of these manuals, bringing out the cultural dimension of the conceptualization of mental disorders.

The current DSM edition claims that individuals suffering from depression must incur five or more of the followed symptoms during the same two weeks period, where at least one of them must be either depressed mood or loss of interest or pleasure:

1. Depressed mood
2. Pronounced decrease of interest or pleasure in all, or almost all activities most of the day, nearly everyday
3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day.
4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
5. Fatigue or loss of energy nearly every day.
6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
7. Diminished ability to think or concentrate, or indecisiveness, nearly every day.
8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

3.3 The cognitive model of depression

Aside from the conceptual characterization of depression, cognitive psychology has offered explanatory models of de depression itself. Beck (1967) exposed a cross-sectional model of depression that highlights the capital role of adverse episodes in the origins of the formation of dysfunctional attitudes, which are integrated into the form of schemas, predisposing the individual to suffer from depression in the future by the continuous repetition of this pathways. The result is unbalanced in the attentional resources, which are biased to the negative internal experiences, cognitions, and sadness, emerging clinically as rumination. Critically, the cognitive schemas behind the attentional bias can be triggered by daily events, inducing mild depression symptoms. Beck claims that this bias's automatic, rapid, and involuntary nature behaves as cognitive filters, reacting to congruent stimuli while ignoring the incongruent inputs (Beck, 2008). Beck also defends that the activation of these cognitive schemas redounds in a standard pattern affecting all the different processing levels, such as attention or memory. The activation of the cognitive schemas triggers the cognitive triad: the individual's negative thoughts about the self, the environment and the future (Beck, 1967).

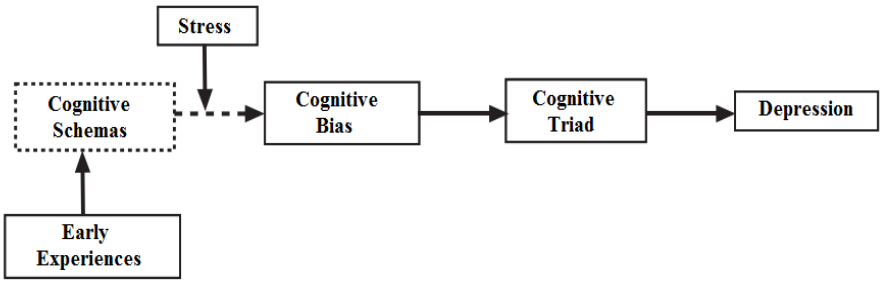


Figure 1.6: schema of the cognitive model of depression proposed by Beck (1967). Taken from Beck (1967).

A similar formulation relying on a dual processing model presented by Beevers (2005) suggests a cognitive vulnerability to depression emerges when the negative biased associative process is uncorrected by reflective processing (Beevers, 2005). This model defends, on the one hand, a fast, automatic associative process that relies on solid associations and a reflective model that depends on the cognitive inferences on the other.

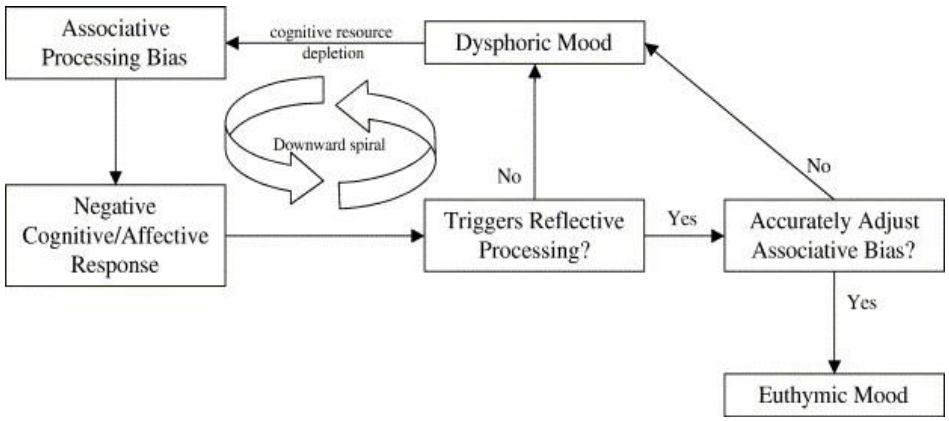


Figure 1.7: schema of cognitive model of depression based on Beck's previous model proposed by Beevers (2005).

Beck's depression model has been refined across years, incorporating more factors from clinical, experimental, and epidemiological evidence of depression. In 2010, Vazquez, Hervás, Hernangómez & Romero proposed an integrative model of depression in which cognitive schemas of depression would not be only preceded by adverse capital episodes but by chronic stressors. Moreover, their model integrates the relevant role of the implicit and explicit self-steem and its variability and consistency as a vulnerability factor of depression. In addition, the interacting role of the ruminative reactions with the cognitive bias in this model is presented as a mediator factor between the cognitive bias and the depressive symptoms. Finally, this model also focuses on the relevance of the cognitive strategies in suppressing reiterative negative thoughts, which instead of attenuating the negative impact of those, seems to increase it (Vázquez C. et al., 2010).

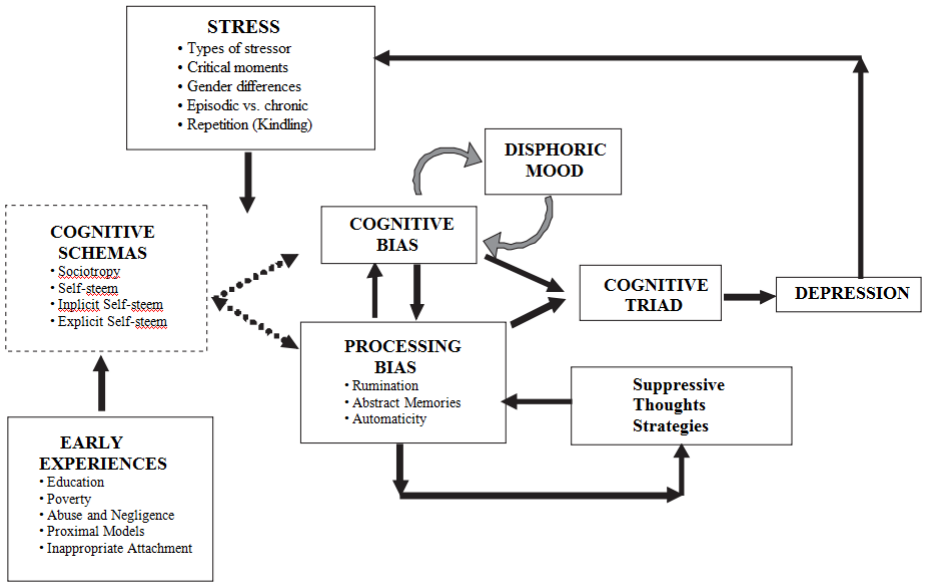


Figure 1.8: depicts the cognitive model of depression proposed by Vazquez et al. (2010) based on the clinical and experimental evidences of the cognitive approach. Taken from Vazquez et al., 2010.

Regarding the heritability impact of depression with respect to cognitive bias, Beck (2008) relates the cognitive vulnerability with the genetic factor (Beck, 2008). Concretely, he based on Caspi et al. (2003) findings where individuals with the short allele variation of the serotonin transporter 5-HTTLPR exhibited higher depressive symptoms and suicide attempts after a recent life stressor. The less effective transcription of the short variant of this gene compared to the more extended variant implicates the hippo-expression of this serotonin transporter, which agrees with the pharmacological treatment of depression with selective serotonin reuptake inhibitors.

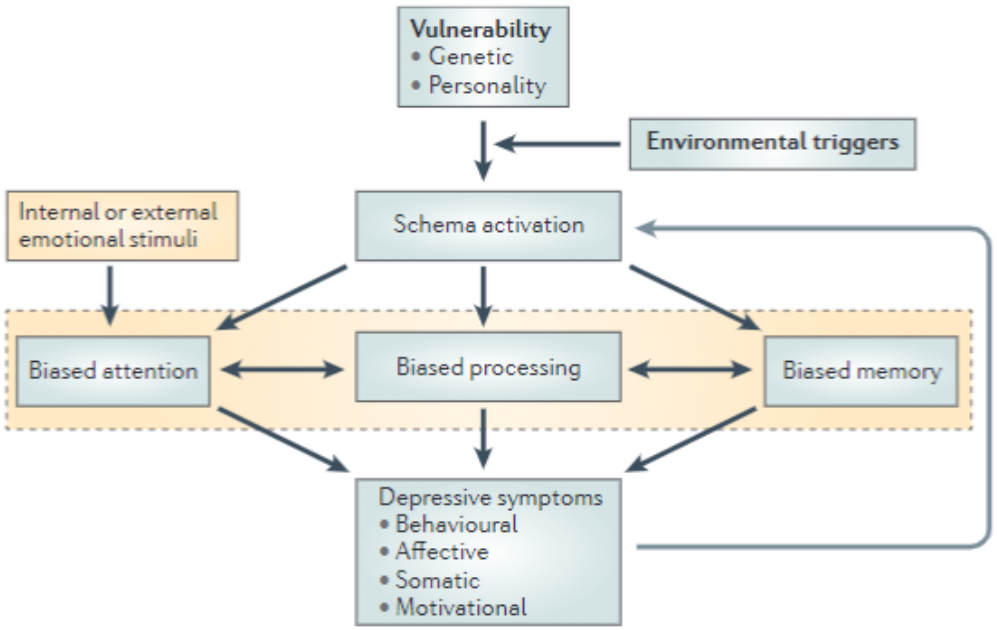


Figure 1.9: The last cognitive model of depression proposed by Beck (2011) based on previous proposed model (1967) where the author includes the genetic load of depression as a risk explicatory factor for suffering from depression. Taken from Beck, 2011.

The short variation of the 5-HTTLPR has also been related to changes in amygdala excitability. However, the mixed direction of this association has been controversial, and it has been pointed out the relevance of the genetic background (such as ancestries) in the study of a single genetic polymorphism: different studies have found opposite directions in the amygdala excitability pattern regarding the East Indian ancestry and the European ancestry sample (see meta-analysis Munafò et al., 2008)). This way, Beck introduces the genetic load of depression as a risk factor for depression in the model, preexistent with the cognitive vulnerability of depression. (Disner et al., 2011)

However, the impact of the so-called ”blue gen” responsible for the predisposition to suffer from depression is still chimerical. Especially taking into account the multifactorial character of depression, where differences on several brain structures have been described in psychophysiology regarding depression (such as the amygdala, the hippocampus, the subgenual anterior cingulated cortex, the ventral striatum, or the dorsolateral prefrontal cortex). Unfortunately, under the current technological restrictions, the attribution of genetic load to the alteration of one single gene seems to be a simplistic focus for a more complex problem. (for further information, see (Hamilton J.P. et al., 2011).

Therefore, instead of focusing on a single gene expression, new approaches in psychophysiology regarding the characterization of the familiar vulnerability of the major depressive disorder are orienting their efforts towards the characterization of a specific endophenotype of the depression (Kayser et al., 2017; Moratti et al., 2015; Rotenberg, 2004; Rottenberg et al., 2005)

4 General Hypotheses

Based on previous evidence of the impaired performance in depression and the impact of the familial load of depression as a vulnerability factor for depression (Beck, 2008; Kayser et al., 2017; Moratti et al., 2015), we hypothesize that individuals suffering from the unipolar major depressive disorder will exhibit impaired motivated attentional processing, reflected by a decreased emotional steady-state modulation when compared to healthy

control subjects under emotional stimuli exposure. Moreover, consistently with previous work (Kayser, 2000; Kayser et al., 2017; Moratti et al., 2004, 2008, 2015; Rotenberg, 2004; Rottenberg et al., 2005), we hypothesize reduced ssVEF responses to emotional stimuli would be primarily located to right temporo-parietal cortex regions.

Regarding the family history of depression, we hypothesize that those individuals with a family history of depression will display a relatively reduced activity increase for emotional stimuli in the right temporo-parietal cortex compared to those without a familial load of depression.

At a peripheral level, based on previous findings of blunted response levels of heart rate variability (Salomon et al., 2013), we hypothesize less peripheral excitability explained by lower heart rate change reactivity during emotional stimulation when compared to healthy individuals. Like the steady-state response, regarding the family history of depression, we hypothesize a relative blunted cardiac response for those individuals with a familial history of depression.

Further, we assume that both impaired responses are related, indexing a lower orienting response at central and peripheral levels. This will be reflected in reduced ssVEF power differences between emotional and neutral pictures in depressed participants accompanies by less triphasic HR modulation (deceleration, acceleration, and deceleration).

Finally, due to the critical role of the amygdala in emotional processing, we will explore the volumetric differences of the amygdala regarding the current status of depression and the presence of the family history of depression. Based on previous works of depression and amygdala volume (see meta-analysis Hamilton et al., 2008), we hypothesize an increased volume of those individuals with current depression status. Likewise, we hypothesize that individuals with a family history of depression will exhibit a relatively increased amygdala volume than those without a familial load of depression.

To this aim, we recruited patients suffering from unipolar depression and healthy individuals as control subjects based on the DSM-IV criteria. Regarding the family history

of depression, we used the Family History Scale (FHS) adapted to the Spanish sample to this aim.

To test the hypothesized differences, we monitored the autonomic and cortical responses during exposure to complex emotional images extracted from the IAPS under MEG-ECG simultaneous recording and analyzed the steady-stated and the heart rate change response during the stimulation.

At the morphological level, we tested the hypothesized morphological differences across experimental groups analyzing the volumetric outcome from the structural MRI scans.

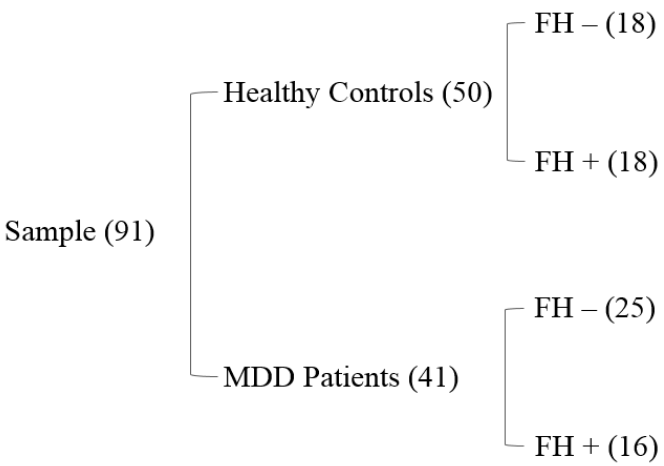
Finally, we explored the eventual relationships between the steady-state response and the cardiac and the volumetric results by correlating the steady-state response with the resulting values from the cardiac and the volumetric analyses.

5 General Material & Methods

Because all the studies presented in the current thesis were developed under the same paradigm and the same inclusion criteria, the Participants and Stimuli sections are minutely described in the current section.

Participants

Ninety-one volunteer participants (67 females, 84 right-handed. Mean age = 30.71; range 18 to 62 years) participated in this study after having given written informed consent and psychological screening. All participants were previously evaluated to determine whether they met the general inclusion criteria for the study and to characterize as healthy participants or MDD patients, with or without a family history of depression for the sample distribution. All subjects had a normal or corrected-to-normal vision. The study had full ethical approval from the local ethics committee for the ongoing clinical project (TEMPACOR). Note that the number of participants per cell can differ across studies due to the lack of known familial load of depression.



Psychological screening

Screening consisted in applying a broad set of questionnaires composed of the General Health questionnaire (GHQ-28), the Hamilton Anxiety Rating Scale (HARS), the Hamilton Depression Rating Scale (HDRS), the semi-structured DSM-IV SCID and the Spanish Adapted Family History Scale (FHS-S)[1]. The psychological screening was administered for each subject before MEG recording, independently from prior psychological diagnose.

General inclusion criteria and sample distribution

Subjects incurring in any mental disorder different from MDD (alone or concomitant) and those with thyroid or any other hormone related diagnosed disorders were not recruited for the study. Those considered for the final sample were distributed across experimental groups according to: (1) Current positive MDD syndrome (n = 41) and (2) presence of first-degree family history of depression (n = 34).

Participants were considered for the healthy control group when (i) they did not meet the DSM-IV criteria for any mental illness and (ii) scoring below 8 in the HDRS, 18 in the HARS and 24 in the GHQ-28. On the other hand, (i) subjects meeting DSM-IV criteria (ii) scored above 18 in the HDRS and below 18 in the HARS were considered for the MDD sample group[2]. Finally, the presence of familial load of depression was determined by the FHS-S.

[1] The language trans-cultural adaptation of the FHS questionnaire for the Spanish sample was explicitly developed for this study under the original author's permission.

[2] DSM-IV SCID criteria prevailed in case of mismatching scoring.

Stimuli and Procedure

Sixty colored pictures were selected from the IAPS[3] (Lang et al., 2005) according to normative arousal and valence dimensions, resulting in 20 unpleasant (ten mutilation and ten attack scenes), 20 pleasant (ten erotic couples and ten familiar scenes) and 20 neutral images (10 household and 10 neutral person scene). Mean normative valence ratings on a 9-point scale were 2.76 ± 0.19 for unpleasant, 4.87 ± 0.05 for neutral, and 7.33 ± 0.13 for pleasant pictures. Mean normative arousal ratings were 6.9 ± 0.07, 2.8 ± 0.13 and, 5.44 ± 0.24, respectively. Accordingly, participants' ratings were highly similar to the normative ratings (valence: 2.05 ± 0.48 for unpleasant, 5.21 ± 0.34 for neutral, and 7.21 ± 0.91 for pleasant pictures; arousal: 7.62 ± 0.61 for unpleasant, 4.39 ± 0.19 for neutral, and 5.48 ± 1.37 for pleas-ant pictures). Selected stimuli did not differ in brightness, contrast, nor color spectra between categories (see Moratti et al., 2004). Visual stimuli were presented in a magnetically shielded chamber by a video projector (Panasonic PT- D7700E) via a mirror system, subtending a 10º visual angle, both vertically and horizontally. Participants were instructed to fixate to a central fixation cross (visual angle 1.6º vertically and horizontally) that was presented throughout the whole experiment during picture presentation. Stimuli were presented in a pseudorandom order (pictures of the same category were not presented more than twice in a row). Each trial consisted of a 6 s presentation of one picture in a luminance modulated mode of 10 Hz, resulting in 60 on-off cycles of 0.05 s each. Intertrial intervals varied randomly from 8 s to 12 s. Subjects performed a passive viewing task whereby 60 images were pseudorandomly presented during the experimental session, divided in two experimental blocks of 20 min. Each picture was presented twice (once per block but within a different order in each

[3] The IAPS picture numbers were: 1050 1120 1201 1300 1930 2050 2070 2080 2160 2165 2170 2190 2200 2210 2230 2311 2340 2341 2360 2381 2440 2480 2570 2850 3000 3010 3053 3060 3071 3080 3102 3110 3130 3530 4650 4651 4652 4658 4659 4660 4664 4670 4680 4690 6260 6350 6510 6540 7002 7009 7010 7020 7030 7040 7080 7175 7233 7235 9070 9405.

block) resulting in 120 trials. After the MEG recording and outside the MEG chamber participants were asked to rate the previously presented stimuli according to valence and arousal dimensions using a computerized Self-Assessment Manikin (Bradley & Lang, 1994).

1 Introduction

1.1 Main classical hypothesis of motivated attention in depression

The genetic load of familial depression as a risk factor for the major depressive disorder has been widely described in psychophysiological literature (Beck, 2008; Kayser et al., 2017; Moratti et al., 2015). On the other hand, structural and functional evidence of abnormalities in the right temporoparietal region has been related to disturbing emotional information processing, resulting in low emotional arousal and blunted cognitive and physiological responses to high arousal events (Kayser, 2000; Kayser et al., 2017; Moratti et al., 2008, 2015). However, it still unknown the role of the familial load of depression in emotional processing. Therefore, the aim of the current study focuses on the eventual impairment of these emotional-related attentional processes related to the familial history of depression and its relationship with the current depression status. The following section introduces some preliminary evidence of the role of the parietal cortex in emotional processing and major depressive disorder under the main conceptual frameworks of MDD.

- Positive attenuation hypothesis

This hypothesis defends the attenuation of emotional processing of pleasant stimuli of MDD patients. Hence, the critical point of depression would result in a systematic impairment of enjoying hedonic processing. Evidence of hedonic processing impairment has demonstrated consistent results on depressed individuals to positive hedonic stimuli on self-report (Pizzagalli et al., 2008; Sloan et al., 2001) and at behavioral (Henriques & Davidson, 2000) and psychophysiological (Dichter et al., 2004) levels. Moreover, Kasch (2002), on the self-reported measure, found evidence of how MDD patients systematically reported lower positive affect and lower behavioral activation consistent with increased anhedonia and heightened negative affect and behavioral inhibition, indicating that the positive attenuation hypothesis can be congruent with an enhanced negative affect in MDD (Kasch et al., 2002)

- Negative potentiation hypothesis

On the other hand, the negative potentiation hypothesis claims for an overestimation and response to those negative affect events, congruent with the current mood of MDD individuals. Opposed to positive attenuation congruent evidence, negative potentiation findings have disembogued on heterogeneous results which, on the one hand, suggest an increased activity during negative affect processing (Sigmon & Nelson-Gray, 1992) and in the other, have found reduced response at central (Foti et al., 2010; Moratti et al., 2008, 2015; Rotenberg, 2004; Yee & Miller, 1988); and peripheral level (Salomon et al., 2009, 2013). Aside from explaining this incongruence across studies, Heller et al. (1997) found evidence of enhanced performance at the right frontal and parietal cortex during emotional processing under emotional exposure of individuals with high levels of anxiety compared with healthy subjects (Engels et al., 2007a, 2010; Heller et al., 1997). As far as high anxiety symptoms, comorbidity in MDD patients is highly related; incongruent results can come out when anxiety levels are not controlled.

- Emotion Context Insenitivity (ECI)

The Emotion Context Insensitivity or ECI is an alternative hypothesis to the depression mood that claims from an evolutionary perspective that MDD is characterized by disengagement and biased against action, opposed to the classical approach of the mood-facilitation hypothesis of the emotional theory, which defends the role of mood as a facilitator of emotional reactivity to congruent stimuli. Based on self-reported tasks after dynamic emotional video visualization, Rottenberg (2005) found that depressed individuals' reactions to sad films were experimental, behavioral and physiologically were highly similar to healthy participants in terms of magnitude. In the same line, depressed individuals tend to evaluate the neutral videos as sadder than healthy participants. Moreover, he found that sad videos reports were lower for depressed individuals when neutral ones were used as a baseline for the sad condition when compared to healthy subjects (Rottenberg et al., 2005).

The reported findings supporting or rejecting these different approaches have provided robust evidence of the impaired brain response in depression. However, these

differences have been usually focused on particular brain regions based on the asymmetric performance of brain activity when comparing anterior vs. posterior or right vs. left. The following section introduces the general statements of the asymmetric performance approach and the relevant findings regarding the major depressive disorder.

- Brain asymmetries

The psychophysiological study of emotion has systematically found inter-hemispheric asymmetries in brain activity patterns regarding emotional valence and arousal during emotional processing. Thus, these differences have also been a cornerstone in the interpretation of the impaired emotional processing during major depression. Under this framework, reduced left frontal performance is associated with a reduction in the positive mood, and complementary, enhanced activity is related with a higher positive mood, while opposite, relative right frontal enhances is related with a predominant bad affect (Heller et al., 1997). This perspective is highly related to the motivated attention theory, which defends the existence of differentiated psychophysiological circuits for both appetitive and defensive systems are related (P. J. Lang & Bradley, 2010)

However, it has also been claimed that the difference in the activation patterns of left and right frontal cortices could be associated with approach and withdrawal motivation tendencies more than pure valence differences. Hence, the left frontal cortex would play a predominant role in the approach responses, while right activation would be related to withdrawal behaviors (Harmon-Jones et al., 2010; Jackson et al., 2003).

A brief review of the evidence found in psychophysiology in major depressive disorder and emotional processing is exposed bellow.

1.2 Right posterior cortex in emotional processing

Heller's neurophysiological model of emotion focuses not only on the frontal asymmetry but also on the right posterior cortex. Several shreds of evidence point to the primary role that the right posterior cortex plays on the high-arousal emotional processing (Heller et al., 1997), like the enhanced activity at the right temporo-parietal cortex in human emotional face expressions (Heller, 1993) and the reduction of skin conductance response to emotional stimuli of patients with damage at right parietal region (Heilman et al., 1978). Accordingly, patients with brain lesions at the left parietal cortex did not exhibit any galvanic response reduction compared to controls, but with those with right parietal brain damage did (Caltagirone et al., 1989).

The chimeric faces test, consisting of presenting split faces, has also been useful in the study of emotional processing. Levy et al. (1983) observed that healthy participants tend to evaluate as happier when the smiling face was located at the left visual hemifield, which is processed in the contralateral hemisphere, supporting the advantaged role of the right temporo-parietal cortex in the emotional processing of emotional faces (Bruder et al., 2002; Levy et al., 1983). Moreover, later evidence showed that depressed individuals did not exhibit the left-biased attention to emotional faces, supporting the right posterior role on emotional processing (Jaeger et al., 1987)

Event-related potentials (EEG) or fields (MEG) such as N1, P1 or P2, have shown differences in the amplitude and the latency of the cortical response in attention paradigm tasks. Critically, Posner-like paradigms allowed researchers to discriminate between attended and unattended stimuli for its comparison. EEG studies have shown greater amplitude of P1 and N1 between 80 and 200 ms when a neutral stimulus where attended than when it was not (Eason, 1981; Hansen et al., 1983; Harter & Guido, 1980).

Differences in short-latency ERPs such as P1 and N1 have also been related to early emotional processing (Carretie et al., 2003; Keil et al., 2001c). Aside, differences in the early posterior negativity (EPN) has been attributed to differences in the arousal, where

highly arousal stimuli elicited broader negative responses between 200 and 300 ms across occipital regions (Keil et al., 2002; Schupp et al., 2004, 2006).

More recent studies of emotional processing and electrocortical activity have pointed to the right parietal cortex. Together with the differences at the autonomic level, Bradley tested the different response patterns according to the different emotional categories at a central nervous system (Bradley et al., 2008, 2012). Concretely, her team found differences in emotional response at a late time window (between 300 and 700 milliseconds), the so-called late positive potential. Moreover, they also discovered that these differences were maximal at the electrodes placed at the right parietal cortex (Bradley et al., 2012; P. J. Lang & Bradley, 2010). Several studies have discovered similar results (MacNamara et al., 2016; Palomba et al., 1997; Pastor et al., 2008; Sabatinelli et al., 2006; Schupp et al., 2000a, 2000b) under-motivated attention paradigms where emotional stimuli were visually presented while EEG activity was measured. These differences in the affective modulation of LPP in the visual cortex have been explained as the potential result of the re-entrant feedback from the amygdale (Keil et al., 2002; Sabatinelli et al., 2006). LPP has also been related to an orienting response, and therefore, its amplitude would be top-down modulated (Bradley, 2009; Schupp et al., 2006). Critically, the LPP has demonstrated resistance to habituation and independent from the stimuli contrast, brightness, complexity, and spatial frequency, emphasizing its sensibility to the affective dimension (Bradley, 2009).

Specifically, some studies have shown strong results under steady-state emotional paradigms (see steady-state section below). Several studies have found greater steady state amplitude response to attended items than the non-attended (Hillyard et al., 1997; Müller & Hillyard, 2000; Müller & Hübner, 2002). Hence, it stands to reason that those items with higher saliency, which would require greater attentional sources, would exhibit enhanced steady-state response. Motivated attention claims that highly arousal stimuli involve top-down facilitation though highly arousal stimuli attract more attention and, therefore, would produce greater steady-state amplitude response than low arousal neutral stimuli. Greater amplitude response for highly arousal stimuli involving the visual cortex and higher brain regions related to attention networks such as right fronto-parietal networks have been

demonstrated for EEG and MEG response (KEIL et al., 2003; Moratti et al., 2004). Gruss et al. (2012) used emotional faces to elicit emotional reactions on healthy participants under a steady-state paradigm finding increased activity at right posterior regions (Gruss et al., 2012), while Moratti et al. reported consistent results with MEG (Moratti et al., 2004).

More recent steady-state paradigm based on rapid visual stream presentation have also shown differences in amplitude regarding the stimuli valence with different complex images at a 4 Hz frequency (Bekhtereva et al., 2018).

1.3 Right Parietal Cortex in Major Depressive Disorder

The implications of the critical role of the right parietal cortex in the emotional arousal processing also extend to the clinical field: It is sensible to think about the eventual relationship between the role of right parietal activity and mood disorder like depression (and vice versa), where the self-reported scales of emotional valence and arousal appears disturbed when compared to healthy controls responses.

As previously mentioned, Jaeger et al. (1987) reported the lack of left attentional bias to emotional stimuli, previously seen on healthy participants (Levy et al., 1983) in patients suffering major depression disorder under a chimeric faces test paradigm (Jaeger et al., 1987). Aligned with it, Robinson observed the relationship between depression and right hemisphere damage in post-stroke patients, where the severity and the probability of suffering from depression symptoms were related to the more posterior brain damage of post-stroke patients with right hemisphere damage. Interestingly, patients with right posterior brain lesions revealed more chronicity of depressive symptoms, while patients with left frontal affection suffered depression only during the acute phase of the stroke (Robinson et al., 1999; Shimoda & Robinson, 1999).

Alpha band studies have also pointed to the right parietal cortex as a key point of depression. These studies found a higher amplitude of the alpha band at the right parietal cortex in depressed individuals when compared to healthy subjects. As far as this method assumes alpha increase as a signature of hypoactivation, it supports the hypothesis of right

temporo-parietal dysfunction in depression and the neurophysiological model of emotion previously mentioned postulated by Heller (Heller et al., 1997).

Nonetheless, it seems reasonable that the best approach to characterize the role of the right parietal cortex in emotional processing and its impaired performance during unipolar major depression is observing the right parietal performance of depressed individuals under emotional processing tasks. ERPs & ERFs have been good candidates for the study of depression due to the possibility of analyzing the brain activity in a specific region during specific task performance. As mentioned above, among the different characterized ERP/Fs, the LPP has demonstrated a well-characterized signature of arousal modulation processing under-motivated attention paradigms and a pretty robust event. A probe of it is the vast amount of replications in studies where high and low arousing stimuli are compared (Cuthbert et al., 2000; Schup et al., 2000; Kayser et al., 2000; Keil et al., 2002; Hugh and Low, 2006; Bradley et al., 2007; Sabatinelli et al., 2007; Pastor et al., 2008).

First evidences of different performance of P300 were reported by Henriques and Davidson (1995), who found reduced P300 wave over the right hemisphere, most pronounced posteriorly in depressed individuals (Henriques and Davidson, 1995). In the same line, Urretavizcaya et al. (2003) found a reduced P300 ERP in depressed individuals under a dichotic listening task, where depressed participants failed to show the previously described P300 wave (Urretavizcaya et al., 2003). In this line, Deldin et al. tested the P3 on depressed patients while black and white emotional faces viewing. They found that depressed patients exhibit a decreased P22 and P300 ERP when compared to healthy subjects during emotional processing. Moreover, they also found that these differences were maximal at posterior regions of right hemisphere (Deldin et al., 2000). Similar results were reported by Kayser et al. (2000 and 2017) in a passive viewing task with low and high arousing emotional images were presented to the participants. Aligned with previous evidence, they found a substantial reduction of the late P300 amplitude and no enhanced LPP amplitude for high arousal stimuli compared to neutral in MDD patients (Kayser, 2000; Kayser et al., 2017). Further, a recent study from Santopetro et al. (2021) revealed that the

reduced P300 performance in adults suffering from major depression predicts the increased severity of depressive symptoms (Santopetro et al., 2021).

Similar results were reported by Foti et al. (2010) under an emotional faces passive viewing task. Reported results demonstrated a blunted response of depressed individuals compared to healthy individuals in the LPP at the right parietal cortex. These results would be associated with reduced emotional reactivity to threatening stimuli, which is consistent with the perspective that emotional reactivity is influenced by the current mood state instead of supporting the ECI hypothesis (Foti et al., 2010).

1.4 Right Parietal Cortex: MDD vs GAD

More pieces of evidence of the relationship of the MDD and the attenuated LPP response while IAPS pictures viewing were reported by Macnamara (2016). Additionally, she compared not only the LPP response in MDD but the general anxiety disorder (GAD). Results showed that whereas MDD was associated with less emotional regulation of the LPP, GAD was associated with increased emotional modulation of the LPP. Moreover, more severe symptoms of MDD were associated with lower LPP modulation, while sharper symptoms of GAD were associated with more significant negative modulation of the LPP (MacNamara et al., 2016). The authors attributed these results as supporting evidence for the emotion context insensitivity hypothesis in the case of MDD and the negative potentiation hypothesis in GAD (MacNamara et al., 2016). Critically, this study supports previous evidence higher levels of right frontal activity under emotional exposure in anxious participants when compared to healthy subjects, where consistently, greater parietal activity for both hemispheres was found in anxious participants, with a greater right parietal activity within this group (Engels et al., 2007b; Heller et al., 1997).

Even when evidence reported by Kayser et al. (2017) showed mismatching results in patients suffering lifetime anxiety, who exhibited an attenuated LPP response during high arousing images viewing, it is still unclear the relationship between high levels of anxiety and current depression status. Therefore, due to the high comorbidity of anxiety symptoms

on MDD, it is mandatory to consider the eventual high anxiety symptoms while studying current MDD (Kayser et al., 2017).

1.5 Right Parietal Cortex & Familiar Risk of Depression

Evidence of the preeminent role of the tempo-parietal cortex in MDD has been robustly demonstrated. However, to date, it is still unclear whereas the right parietal impairment is due to the current status of MDD patients or could be explained as a risk factor of depression due to the presence of a family load of depression.

While evidence like Macnamara (2009) supports the idea of right parietal impairment during lifetime depression, evidence like Robinson and Shimoda (1999) suggests that this impairment could be read as a risk factor of depression.

EEG studies based on the alpha power analysis during resting state have related the alpha power activity at the right parietal cortex to the high risk of depression. (Bruder et al., 2005, 2007, 2012; Peterson 2009; Talati et al., 2013; Kayser et al., 2014). Under this framework, alpha is considered an inverse index of cortical activity, where increased power is related to lower activity.

Interestingly, Tatali reported decreased alpha activity at the tempo-parietal cortex in individuals with a high risk of MDD compared to low-risk participants. Aligned with previous evidence of the correlation of the decreased EEG activity and cortical thinning (Bruder et al., 2012) and cortical thinning at the right temporo-parietal cortex on individuals with a family load of depression (Peterson et al., 2009), he also related these findings with the cortical thinning at this specific region, suggesting that these differences would suppose a risk factor of MDD (Tatali et al., 2013).

Based on previous evidence of MDD and the family history of depression, Moratti et al. (2008) tested the role of the right temporo-parietal cortex in the depression under a ssVEF paradigm, where participants' bio-magnetic brain responses were recorded during IAPS emotional complex scenes viewing flickering at a certain frequency of 10 Hz. Due to the

spatial resolution of the MEG and the high signal-to-noise of the ssVEF paradigm, this study had a preponderant advantage in the characterization of the temporo-parietal cortex role in MDD. Results depicted the decreased ssVEF amplitude response in MDD patients compared to healthy subjects during arousal modulation (Moratti et al., 2008). Critically, in a subsequent study, Moratti et al. (2015) included the Familiar history of depression as a variable within the MDD group, finding that those individuals with a family history of MDD exhibited lower oscillatory response for high arousal images when compared to those without a family history of depression at the right temporo-parietal cortex, suggesting the impairment in this region as a potential candidate of endophenotype of depression (Moratti et al., 2015). However, despite the strong evidence of the relationship between right temporo-parietal and the family load of depression, family history was considered only within the MDD group.

Kayser et al. (2017), based on prior evidence of participants with high-risk of MDD in LPP response and brain asymmetries under high arousal picture viewing (Kayser et al., 2014), developed a similar EEG study analyzing the eventual influence of familial risk for depression, as well as lifetime diagnosis of MDD or anxiety disorder (Kayser et al., 2017), where, consistently with Moratti (2015), found a decreased LPP response in high-risk participants. Interestingly, these results were comparable to the lifetime depression participants, supporting previous evidence of weaker emotional responsitivity under MDD and a familial load of MDD conditions. Interestingly, they found no significant differences in valence and arousal self-reported ratings, suggesting that risk status did not alter the conscious experience of the aversive stimuli (Kayser et al., 2017).

In sum, it seems like cortical attentional networks and top-down motivated attentional processes are not adequately performing in the current depression status. Moreover, recent evidence in the study of MDD heritability points to the right temporo-parietal impairment as a potential candidate of endophenotype of depression which should be considered for future research on MDD

1.6 Magnetoencephalogram

1.6.1 Considerations on MEG signals

Magnetoencephalography (MEG) is a functional neuroimaging technique focused on detecting and measuring magnetic fields resulting from the biomagnetic activity derived from electrocortical activity. Critically, MEG measures and records the biomagnetic fields derived from the postsynaptic activity located at the apical dendrite of the pyramid neurons primarily located at the layer V of the brain cortex.

The three main electrical current generators that can be found behind cortical activity are originated by the action potentials, the postsynaptic potentials, and those located in the dendritic hendidura. Due that the last ones result too small to be detected and its random spatial distribution generates magnetic cancelation, the electrical activity produced in the dendritic hendidura is invisible for the Magnetometers. On the other hand, the action potentials result too fast (< 2 ms) for the eventual coactivation in time, making impossible the spatial summation necessary to produce a powerful enough signal to be measured by the sensors (Maestú et al., 2008). However, the excitatory (around 80%) and inhibitory postsynaptic potentials generated in the apical dendrites perform a more extended time duration (over tens of ms), making possible the synchronization and the consequent generation of a measurable magnetic field.

Even when the temporal summation is a necessary condition for the measurable signal generation, it is not sufficient: for the spatial summation of the postsynaptic potentials, these (a) must be disposed on parallel and (b) must be open-field neurons: opposed to the close-field neurons which apical dendrite is disposed of in parallel, the open-field neurons present a tangential dendrite, allowing the isolation activity of the dendrite from the rest of the neuron.

The parallel disposition of the dendrites is given by the accommodation of the pyramid neurons within the cortical layer, keeping the same orientation of the fields and making possible the spatial summation instead of canceling each other (Lopes da Silva, 2013;

(Hämäläinen M., Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Murakami & Okada, 2006).

The orientation of the cortex itself with respect to the skull also plays a role in the MEG; given the tangential disposition of the pyramid neurons to the cortex, those located in the cortical gyrus would produce perpendicular electric currents and congruent parallel magnetic fields, while those distributed among cortical sulci, would generate tangential fields respect to the sensors. Therefore, it is easier for the MEG to localize activity coming from the sulci rather than that originated in the gyrus.

Given the minimal amplitude of the magnetic field produced by a single neuron, MEG depends on the magnetic summary properties (temporal summation of potentials) to detect and measure biomagnetic postsynaptic activity. Concretely, it is necessary the synchronized activity from at least a 10^5 neural population, resulting in an intensity flow of at least 10nA, able to generate an associated magnetic field of 100 fT (Lorente de No, 1947) spread over 4 cm radius-distance from a sensor, generating power enough for being detected.

1.6.2 Technical concerns about MEG recordings

From a technical point of view, MEG highlights the high temporal (over 1000 Hz sample rate) and spatial resolution (around 10 mm), given that magnetic fields do not differ when crossing different tissues, such as cephaloraquideus liquid, meninges bone, or skin. Besides, its non-invasive character supposes a decisive advantage compared to other functional techniques in neuroimaging, such as positron emission tomography (PET) or intracranial electroencephalography (iEEG). On the other hand, having a similar sampling rate to the EEG, MEG excels in the spatial resolution, whereas its high temporal resolution allows faster cortical processes measurements than the functional magnetic resonance imaging (fMRI). Finally, MEG exhibits a robust signal-to-noise ratio, especially above 45 Hz.

Despite the high performance of the MEG as functional imaging technology, it presents some challenges: first of all, its extremely high sensitivity on detecting changes on the

magnetic fields, it is not possible to record human brain activity outside of an isolated chamber recovered by high permeable μ-metal, which provides a magnetic attenuation between 90 to 130 dBs for 1 Hz. Moreover, the presence of any ferromagnetic metal in the subject itself or any muscular movement precludes the recording, which supposes a particular impairing issue regarding the participants recruiting.

Even under the absence of ferromagnetic noise, before preprocessing MEG signal must be filtered by applying a Temporal-Spatial Signal Space Separation (Taulu & Simona, Maxfilter 2.2. software, 2006). (Further preprocessing requirements necessary are specified in the methods section of the current chapter of chapter). Additionally, Magnetometers can only detect the tangential magnetic fields, being blind to those disposed in parallel (figure).

Finally, due to the resulting cancellation of opposed magnetic fields, MEG results are also incapable of detecting activity originated in spheric-shaped human brain structures and deep brain sources, such as the basal nuclei.

1.7 The steady-state Paradigm

1.7.1 The *steady-state* Visual Evoked Potentials/Fields (ssVEP/ssVEF)

The steady-state visual evoked potentials (ssVEP) in Electroencephalography (EEG) or fields (ssVEF) in magnetoencephalography is a specific paradigm of visual stimulation based on the averaged response of a sequence of visual evoked potentials (VEP) or fields (VEF). Unlike the classical ERPs paradigms, where the aim is to record the individual's response to an isolated event triggered by a discrete stimulus compared to a pre-stimulus baseline, steady-state paradigm analysis depicts the individual overlapped response to the whole stimulation sequence.

First ssVEP were described by Regan in 1965, over thirty years after the first VEP was recorded by Adrian and Matthews in 1934. ssVEPs were described as "a series of potential waves having the same frequency as that of the flicker light" Adrian & Matthews, 1934).

The steady-state paradigm aimed to find a more excellent signal-to-noise ratio, obtaining a repetition frequency with a lack of contamination from any other frequencies and, therefore, making possible the study of isolate perceptual characters, such as color. However, the neural performance behind the ssVEPs is still controversial; whereas ssVEPs are understood as a concatenation of isolated VEPs (Capilla et al., 2011), ssVEPs have been argued to represent resonant behavior of damped neural oscillators (Bayram et al., 2011).

However, due to the phase and amplitude stability over time, Regan named this ERPs steady state VEPs (Regan, 1965). Because of its periodic character stability at a specific frequency, the ssVEPs are analyzed in the frequency domain (Hz) and magnitude response. Accordingly, Norcia considers that "what is critical for the definition of a response as an SSVEP is not the temporal frequency of the stimulus but rather the fact that the stimulus and the response are each periodic" (Norcia et al., 2015).

First recorded ssVEP consisted in an on-off pattern modulated by contrast; this way, the neural mechanism sensitive to the on-off steady-state response could be specifically attributed to the spatial contrast (Spekreijse et al., 1973). The critical point behind the contrast modulation is to control all the low-level features to isolate the specific feature we want to test. However, whereas this logic is essential for low-level feature studies, the approach differs for higher-level patterns (like complex emotional faces), where the contrast between on and off cycles should not be necessarily controlled (Norcia et al., 2015).

1.7.2 ssVEP in higher level processing

Because the maximal ssVEP response is usually located over the medial occipital lobe, it is originated at the primary visual cortex (Müller et al., 1997; Di Russo et al., 2007), steady-state paradigms have usually been implemented under lower-level visual processes framework. However, steady-state paradigms have also been used in the study of higher-level processes, such as memory encoding, fear conditioning of emotional processing (Keil 2010, Moratti 2014, Müller 2018).

We find two main approaches regarding the higher-level processes' analysis: the indirect approach focuses on the differences in the low-level visual areas related to higher-level processes. This approach assumes the top-down modulation of higher-level processing regions in the lower-level processing areas performance, such as the previously mentioned primary visual cortex (Müller et al., 1997). In this approach, the whole brain activity is analyzed within the same frequency sample. On the other hand, a direct approach paradigm allows the researcher to isolate the higher-level activity response from the low-level visual.

Visual reactivity to the ssVEPs encompasses a wide range of frequencies, but usually, these frequencies are between 3 and 20 Hz (Norcia et al., 2015). Critically, the maximal response attributed to ssVEP is at 10 Hz, the reason why several studies focus on this specific frequency (Gruss, Wieser, Schweinberger, & Keil, 2012; Kaspar, Hassler, Mar-tens, Trujillo-Barreto, & Gruber, 2010; Keil et al., 2003; McTeague, Shumen, Wieser, Lang, & Keil, 2011; Moratti, Keil, & Stolarova, 2004; Moratti et al., 2015; de Echegaray and Moratti, 2021). Usually, lower stimulation frequency rates are more likely to be used in studies with more complex stimuli paradigms. Critically, the Müller laboratory (2018) has reported a reversal effect of the ssVEP amplitude during complex emotional scenes viewing between 4 and 6 Hz in a cross-laboratory study, where the 4 Hz stimulation frequency revealed greater activity for emotional content whereas ssVEP amplitude decreased at 6 Hz stimulation frequency (Bekhtereva et al., 2018). These results were found under a specific steady-state paradigm, the so-called rapid serial visual presentation (RSVP), where a stream of different images is visually presented, eliciting the ssVEP response. Interestingly, this kind of paradigm is believed to produce both back and forward masking of each image for the previous and the subsequent scene (Bekhtereva et al., 2018).

Finally, the tagged ssVEP response to a specific frequency allows the researchers to present different target stimuli at different stimulation frequency rates. The presentation of multiple inputs allows the ssVEP testing under a competition scenario. A good example is the study of the spatial distribution of attention under a classical Posner paradigm, where two stimuli presented at opposed visual hemifields competing for the attentional resources (Posner, 1980).

The multi-input paradigm also made possible the study of the distributed attention to a specific feature, such as movement, color, or direction. Müller et al. (2006) described a smart method to study the feature-based attention where participants had to pay attention to a particular feature among a cloud of red and blue dots flickering at different frequency rates (Müller et al., 2006). This feature-based attention paradigm has been implemented in more complex experimental scenarios such as the Posner paradigm, where four different frequencies are presented.

The frequency tagging and the robust signal-to-noise ratio make the ssVEP-F a powerful experimental source in the study of the motivated attention.

1.8 Hypotheses

Based on the previous evidence, we hypothesize that depressed patients will exhibit a decreased steady-state Visual Evoked Fields (ssVEF) amplitude modulation (higher power for emotional pictures) under emotional exposure compared to healthy control subjects. We also hypothesize that this reduced amplitude modulation will be maximal in the right temporo-parietal cortex. Moreover, we hypothesize that this down-regulation will be more pronounced in the presence of familial load of depression for both, healthy controls and depressed patients, reflecting an impaired emotional-processing response within the temporo-parietal cortex and the attentional brain network in the presence of familial load of major depression.

2 Materials and Methods

2.1 Participants

Seventy-seven volunteer participants (56 females, 72 right-handed. Mean age = 30.71; range 18 to 62 years) from the whole original sample of ninety-one experimental participants participated in this study after having given written informed consent and psychological

screening. Those participants which familial load of depression was unknown were not included in the current study (see general methods).[4]

For more detailed Participants and Stimuli and Procedure information, see General Methods.

2.2 Data acquisition and Preprocessing of MEG data

MEG data of fifty-four participants among the seventy-seven whole sample were recorded at the Laboratory for Cognitive and Computational Neuroscience, at the Center for Biomedical Technology (CTB, Madrid, Spain). The MEG was recorded continuously at a rate of 600.00 Hz (on- line band- pass filter of 0.1- 200Hz), using a 306 channels whole-head system (VectorView© Elekta Neuromag Oy, Helsinki, Finland 2005). For artifact monitoring, the electrooculogram (EOG) was recorded with electrodes attached above, below, left to, and right to the outer canthus. The electrocardiogram (ECG) for heart rate assessment was recorded with electrodes placed at the left mid-clavicle and lower right rib bone. Additionally, one electrode was attached to the left earlobe serving as the ground electrode. EOG and ECG were recorded simultaneously using standard Au electrodes (NSC Electromedicina). EOG and ECG were recorded using the same sample frequency and on-line filters as the MEG data.

Twenty three out of the seventy-seven participants were previously recorded using a 148-channel whole-head system (Magnes 2500 WHS, 4- D Neuroimaging, San Diego, USA). Data of these subjects have been published in a previous study (Moratti et al., 2015). Data of these participants had been recorded at a sample frequency of 254.3 Hz and applying an online filter of 0.1 to 60 Hz. In order to apply the same preprocessing and source localization procedures as in the new sample, data have been up-sampled to 600 Hz using

[4] Participants for that the familial load of depression could not be determined were not included in the present study.

a cascade algorithm as implemented in Brainstorm (https://neuro image.usc.edu/brainstorm/) using the signal processing toolbox of MATLAB (MathWorks©). However, task, experimental design, psycho-logical evaluation, preprocessing, and source localization (see below) did not differ from the fifty-four subjects that were recorded with the Elekta system. As the Magnes 2500 WHS system is equipped with magnetometers only, only magnetometer data from the Elekta system were considered for further analysis. Ashrafulla et al. (2011) have shown that MEG data from different recording systems are comparable when using the minimum norm estimation for cortical source localization.

Eyeblink and heartbeat noise were corrected by Independent Component Analysis as implemented in the Brainstorm toolbox (ICA- JADE). Noisy trials due to movement artifacts and horizontal eye movements as monitored by the EOG were determined by visual inspection and excluded from the analysis. Then, MEG data were digitally band-pass filtered between 1 and 40 Hz (60 dB stop- band attenuation) before averaging pictures by categories (pleasant, unpleasant and neutral) across the 6 seconds post- stimulus interval subtracting a 0.5 s pre- stimulus baseline. Finally, the averaged epochs were submitted to a moving-window averaging procedure, in which a 1 second window containing 10 cycles of a 10 Hz oscillation was shifted across the epoch in steps of 0.1 seconds (see for example Yuan et al., 2018). All preprocessing was performed using the Brainstorm toolbox (Tadel et al., 2011).

2.3 Cortical Source Analysis of ssVEF

Cortical source reconstruction from ssVEF response were estimated using the Brainstorm open-source-package (http://neuroimage.usc.edu/brainstorm/Tadel et al., 2011) using a canonical cortical surface mesh (7001 vertices) from the Montreal Neurological Institute (MNI) phantom brain (Collins et al., 1998). The individual head and sensor positions of each subject were co-registered with the template brain by realigning the individual with the template brain's fiducial points and minimizing the mean distance between the individual head shape points and the template brain scalp surface (Moratti et

al., 2011). Thereafter, the forward model was calculated by a head model based on overlapping spheres (Huang et al., 1999). Finally, a weighted Minimum Norm Estimation (wMNE; Gramfort et al., 2014) was used to calculate the current density of the ten 10 Hz cycles previously extracted by the moving window averaging procedure (see above) on the cortical surface for later analysis. Amplitude (square root) from resulting averaged volumes transformed to MNI space volumes by brainstorm was estimated before mean-corrected in order to get comparable measurements across subjects. Finally, resulting MNI volumes corrected by the overall mean across all conditions were normalized by subtracting the neutral condition for each experimental condition (Unpleasant = unpleasant – neutral; Pleasant = pleasant – neutral; Arousal = (pleasant + unpleasant)./2 – neutral) before statistically compared with the SPM software (http://hdl.handle.net/2268/153318).

2.4 Statistical Analysis

The interpolated 3D volumes representing the 10 Hz amplitude of the ssVEF brain response in cortical source space resulting from the cortical source estimation, were tested for interaction across conditions from the resulting four experimental groups as a function of the MDD and the FH factors in an SPM (Statistical Parametric Mapping) ANCOVA model, where age of participants were corrected by including it as a covariate of the analysis. Resulting clusters from ANCOVA analysis were only considered significantly different using a height threshold of $p < 0.01$ and over an extension greater than 100 voxel size as usual criteria to declare significant topographies.

In order to estimate if the significant differences attributed to the SPM ANCOVA may be modulated by anxiety, an additional SPM ANCOVA including the HARS values for each subject was performed for which no differences with the previous one appeared, demonstrating that the interaction effect is not derived or masked by the eventual anxiety symptoms of the current sample.

Post hoc reported analyses from resulting SPM ANCOVA differences were tested by two samples t-test contrast ($p<.05$) of ANCOVA age-adjusted data.

The main effect of depression was estimated by a SPM two samples t-test in from the age-adjusted data from the subjects by including the age of participants as a covariate. Same as ANCOVA, resulting clusters from ANCOVA analysis were only considered significantly different using a height threshold of $p < 0.01$ and over an extension greater than 100 voxels size. Prior to main effect analysis, sample groups distribution was tested by chi square test in Matlab software, where no differences resulted from the analysis.

3 Results

3.1 Arousal modulation: Interaction Family History and MDD

The arousal modulated ssVEF power interpolated into MNI aligned volumes ([unpleasant + pleasant]/2 – neutral) were submitted to an ANCOVA with two between subject factors (depression vs. control and FH+ vs. FH-) and a covariate of age.

Figure 1.1.a shows the significant clusters resulting from the SPM ANCOVA, reflecting the interaction of the family history of depression and major depressive disorder factors in the ssVEF arousal modulation ($F(3,68) = 4.083$, $p<.01$, $k=100$ voxels). The age of the participants was introduced as a covariate in the current analysis.

The principal cluster distribution from caudal to rostral brain areas includes the right superior parietal cortex, the right precentral gyrus, the right middle frontal gyrus, and the left superior frontal cortex (figures 2.1.1 and 2.1.2). The post hoc analysis revealed the significantly higher ssVEF activity for the high emotional arousing pictures in healthy participants with family history of depression compared to those without in right parietal cortex ($t(34) = 3.17$; $p = .003$) (figure 2.1.2.a) and left superior frontal gyrus ($t(34) = 2.72$; $p = .010$) (figure 2.1.2.b).

No significant differences were found in family history within the MDD group in right parietal cortex ($t(39) = 1.02$; $p = .311$), right precentral gyrus ($t(39) = .81$; $p = .421$), right

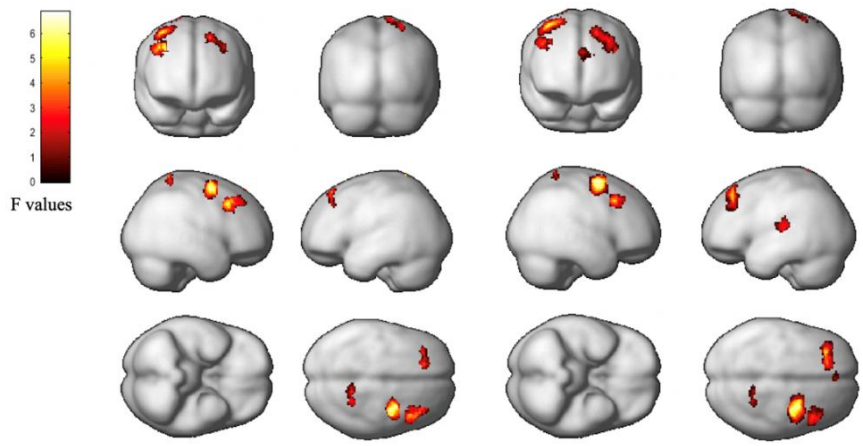
middle frontal gyrus (t (39) = .55; p = .581) and left superior frontal gyrus (t (39) = 1.41; p = .165) (figures 2.1.2.a to d).

Opposed to prior evidence of the decreased activity in this region in depressed patients when compared to healthy individuals (Kayser et al., 2017; Moratti et al., 2015), the higher activity in this region has been related to higher levels of anxiety (Heller, 1997, Macnamara, 2016). Therefore, an additional SPM ANCOVA, including the anxiety levels (HARS scores), was compared to the previously reported SPM ANCOVA. However, the resulting SMP ANCOVA showed no differences as a function of the anxiety levels. Therefore, we conclude that the anxiety levels did not modulate differences in the oscillatory ssVEF amplitude for high arousing emotional pictures in the current sample (figure 2.1.1.b).

Figure 2.1.2.c shows the opposite trend, where healthy controls without a family history of depression exhibit higher activity than those with family history in the right middle frontal gyrus (t (34) = 2.44; p = .019) and both family history positive and negative depressed patients did not differ in ssVEF arousal modulation (t (39) = .55: p = .581).

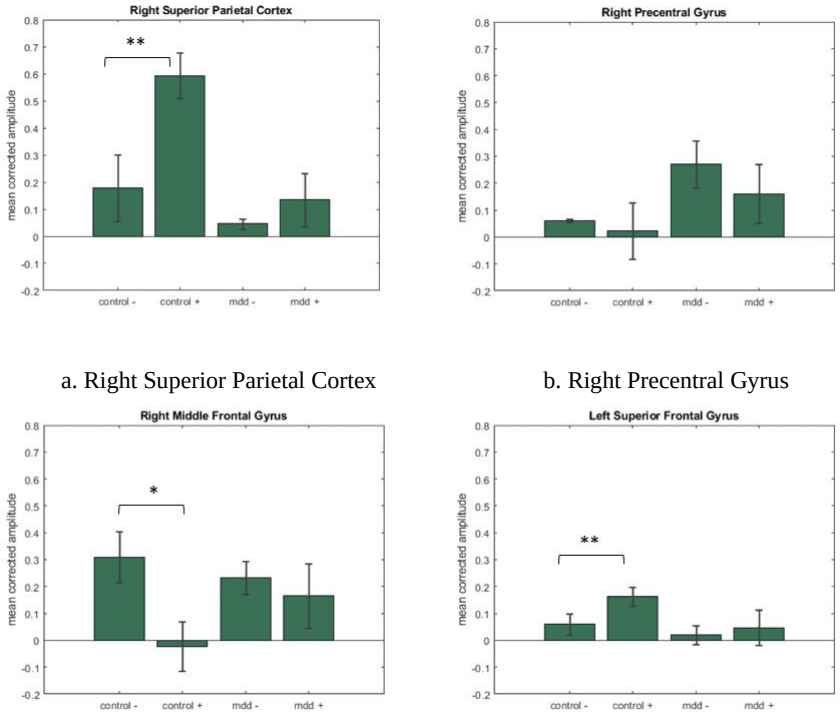
To explore the eventual relationship between the opposed activity direction in the right frontal and the right parietal cortices, the correlation between the amplitude of these regions was tested for each experimental group (healthy participants with and without a family history of depression) in an exploratory analysis. The results show a non-significant negative tendency in the correlation for the FH- group (r=-.334; p=.174) between right frontal and right parietal activity (figure 2.1.3). The correlation between the left frontal – right parietal ssVEF modulations was discarded (r=.458; p=.054) despite the almost significant tendency due to outliers' effect.

On the other hand, no significant right frontal-right parietal correlation was found for the FH+ healthy individuals (r=.37; p=.137), but for the left frontal – right parietal ssVEF arousal modulation (r=.71; p<.001) (figure 2.1.3.b). Additionally, no significant negative correlation between left and right frontal cortex ssVEF amplitude was found within the control group (FH-: r=.32; p=.18 and FH+: r=.32; p=.18) (figure 2.1.3.a).



a. SPM ANCOVA age-correted b. SPM ANCOVA anxiety covariated

Figure 2.1.1. Figure a and b both illustrate the SPM ANCOVA (F (3,68) = 4.083, p<.01, k=100 voxels) for the arousal modulation ssVEF magnitude from the four resulting groups of the FH and the MDD factors. Figure 2.1.1.a shows the resulting topoplot including the age of the participants as covariate, while figure 2.1.1.b depicts the resulting topoplot including the anxiety levels of each participant (estimated by the HARS) as a covariate. Note that the topographic distribution of the significant clusters does not change when the anxiety is included as a covariate, suggesting the lack of impact of it within the current result.



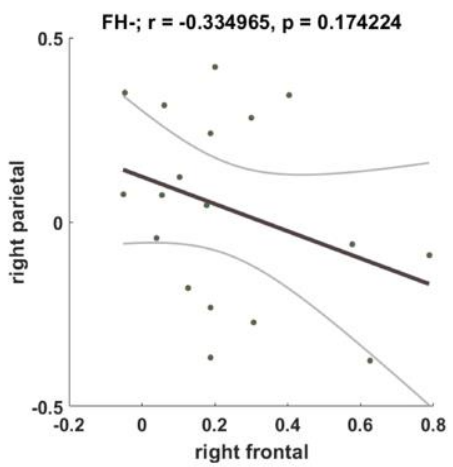
a. Right Superior Parietal Cortex

b. Right Precentral Gyrus

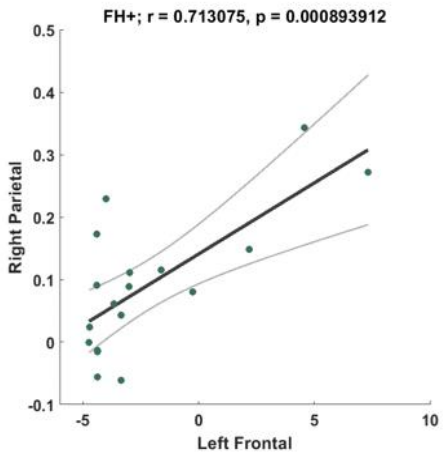
c. Right Middle Frontal Gyrus

d. Left Superior Frontal Gyrus

Figure 2.1.2. *a* to *d* illustrate the mean (bar plot) and the standard error (error plot) of each experimental group (from left to right: Control | FH-; Control | FH+; MDD | FH-; MDD | FH+) resulting from the SPM ANCOVA analysis (F (3,68) = 4.083, p<.01, k=100 voxels) for the arousal modulation ssVEF magnitude. Note that the direction of the interaction shows significant differences within the control group regarding family history of depression factor (FH), where FH+ exhibit greater ssVEF amplitude in the right parietal (a) and left frontal (d) while ssVEF amplitude is decreased at the right middle frontal (c). No significant differences within the depressed group. No significant differences within the depressed group. *Note: * <.01; ** <.001.*



a. Control | FH- Group



a. Control | FH+ Group

Figure 2.1.3. *a* and *b* illustrate Scatter plots of the ssVEF magnitude adjusted by age in the control group's right parietal and right frontal without a family history (a) and the right parietal and left frontal in the control group with a family history of depression (b). Green dots represent individual data points, while the black line indicates the regression slope for the adjusted data, whereas grey lines depict the 95% confidence interval. The correlation coefficients estimate the linear relation between the ssVEF adjusted amplitude between both cortical regions.

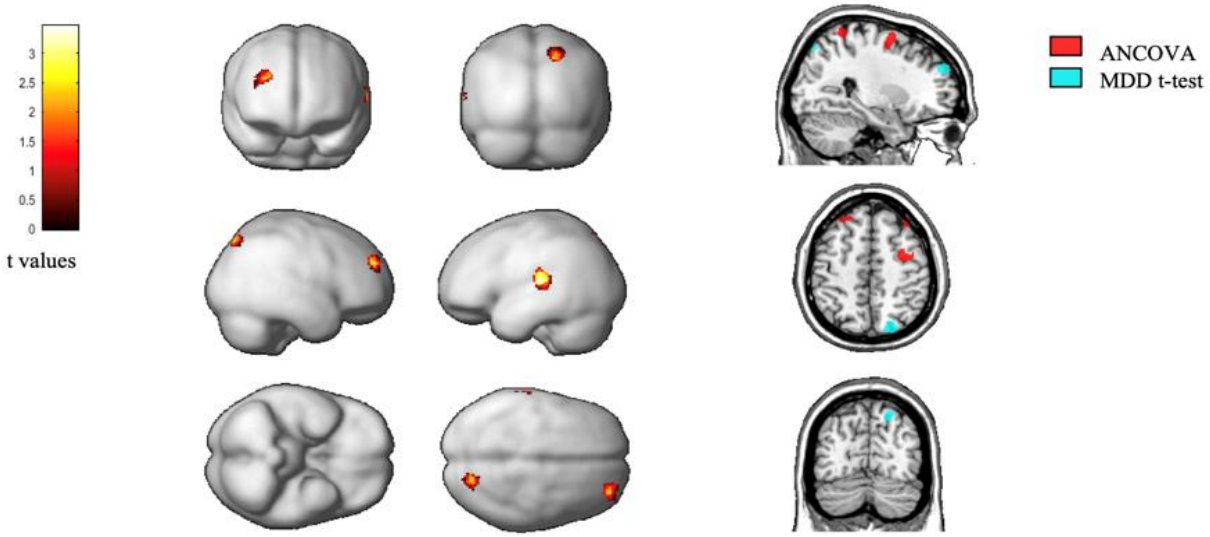
3.2 Arousal modulation: main effect of MDD

Prior to the analysis of the main effect of depression, Chi-square (x^2) test was run to test eventual differences between groups due to the family history status. There were no differences between healthy controls and depressed patients with respect to family history load (x^2=.936; p=.333).[5]

Figure 2.2.a shows the significant clusters resulting from the SPM t-test of the ssVEF arousal modulation between healthy controls and MDD patients ($t(68) = 2.382$; $p < 0.01$; K=100 voxels). Two significant clusters emerged in the right hemisphere at the right superior parietal cortex (figure 2.2.c) and the right superior frontal gyrus (figure 2.2.d). Unlike the interaction map, we find an additional significant cluster in the left central operculum (figure 2.2.e).

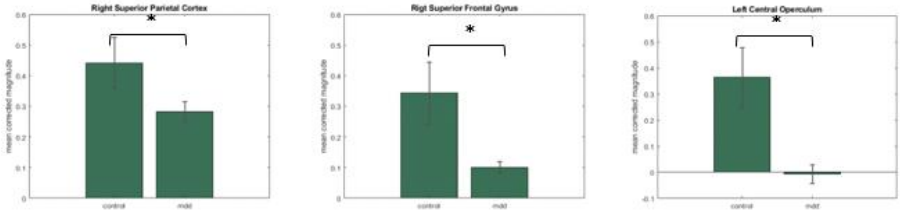
Figure 2.2.b illustrates the significant clusters for the previously reported ssVEF SPM ANCOVA (red) and the t-test for the depression main effect within one SPM. Critically, the significant clusters of the interaction and main effects do not overlap, which points to a different neuronal network behind the emotional modulation under current depression status and the familiar depression background.

[5] Because the experimental groups did not change across arousal, unpleasant and pleasant analysis, x^2 did not differ. Hence, the same analysis routine was used for arousal and unpleasant conditions.



a. SPM MDD t-test topo plot

b. Topographic comparison ANCOVA vs MDD t-test



a. Right Superior Parietal Cortex b. Right Superior Frontal Gyrus c. Left Central Operculum

Figure 2.2: SPM t-test contrast between healthy control (left) and MDD (right) group in arousal modulation ssVEF adjusted magnitude including the age of the participants as covariate ($t(68) = 2.382$; $p < 0.01$; K=100 voxels) (a). Although t-test reveals right frontal and parietal cortices (a) represented in blue (b), there is no overlap with the ANCOVA main clusters represented in red (b). Bar plots illustrate the mean and the standard error of each healthy control and depression groups, where the last exhibit decreased activity in the right superior parietal, right middle frontal and left central operculum (c-d-e). *Note: * <.01; ** <.001.*

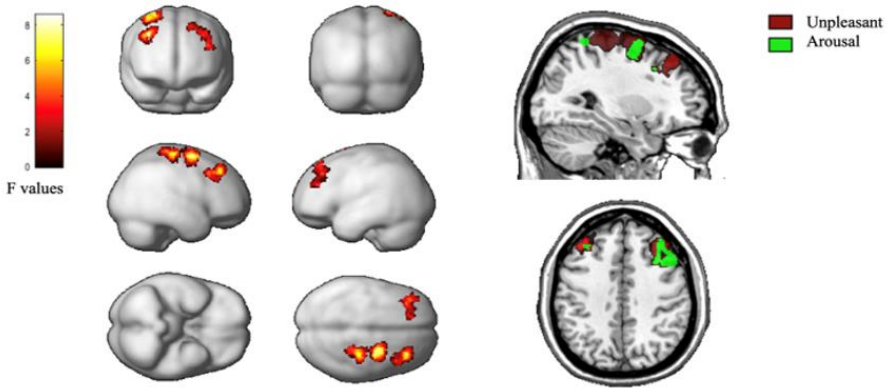
3.3 Modulation by Unpleasant Pictures: Interaction Family History and MDD

Here, we isolate the emotional modulation for unpleasant valence using the neutral condition as a baseline for each emotional category (unpleasant – neutral) at a second-level analysis. Figure 2.3.a displays the interaction test SPM ANCOVA across experimental groups according to depression and family history of depression ($F(3,38) = 4.08$; $p<.01$; $k = 100$ voxels). The principal cluster distribution from caudal to rostral includes the right postcentral and precentral gyrus and the right and left middle frontal gyrus (figures 2.3.a-c-d-e-f).

Similar to the resulting cluster distribution from the arousal ssVEF modulation, current results show an interaction effect within the fronto-parietal network, with higher activity for the healthy participants with family history of depression in the right post ($t(34) = 2.68$; $p = .011$) and pre central gyrus ($t(34) = 2.68$; $p = .011$) and the left middle frontal gyrus ($t(34)$; $p = .002$) when compared with those healthy participants without family history of depression (figures 2.3.c-d-f).

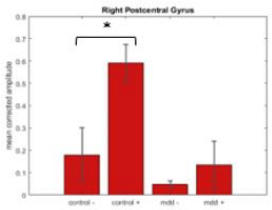
Results showed the same opposite direction of the ssVEF amplitude at the right middle frontal gyrus for the interaction of depression status and family history for unpleasant minus neutral pictures, where healthy individuals with a family history of depression exhibit a decreased activity when compared to those without familiar depression load ($t(34) = 2.57$; $p = .014$) (figure 2.3.e).

No significant differences were found in family history within the MDD group at post central gyrus ($t(39) = .26$; $p = .795$) and pre ($t(39) = .28$; $p = .780$) and left middle frontal gyrus ($t(39) = 1.99$; $p = .053$) (figures 2.3.c-d).

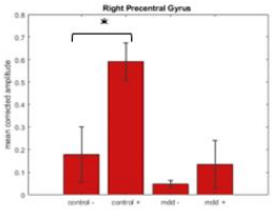


a. SPM ANCOVA agecorrected

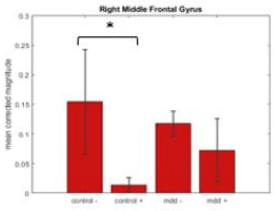
b. Topographic comparison
Arousal vs Unpleasant ANCOVAs



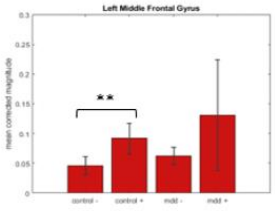
c. Right Postcentral Gyrus



d. Right Precentral Gyrus



e. Right Middle Frontal Gyrus



f. Left Middle Frontal Gyrus

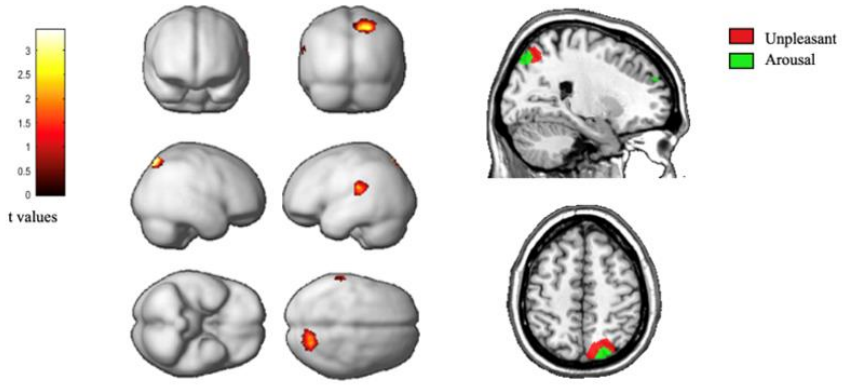
Figure 2.3: SPM ANCOVA unpleasant modulation (unpleasant - neutral) ssVEF adjusted amplitude including the age of the participants as covariate ($F(3,38) = 4.08$; $p<.01$; $k = 100$ voxels) (from left to right: Control | FH-; Control | FH+; MDD | FH-; MDD | FH+). (a) represented in garnet (b) shows partial overlap with left and right frontal clusters resulting from arousal modulation SPM ANCOVA represented on green (b), but not for the right parietal cortex. Bar plots illustrate the mean and the standard error values of the ssVEF adjusted amplitude of each experimental group regarding the main factors *depression* and *family history of depression* for each significant cluster resulting from the ANCOVA interaction analysis (c-d-e-f). Note that similar to the arousal modulation ANCOVA, the direction of the interaction shows significant differences within the control group regarding FH factor, where FH+ exhibits greater ssVEF amplitude in right pre and post-central gyrus and left frontal while ssVEF amplitude is decreased at the right middle frontal. No significant differences within the depressed group. *Note:* * *<.01;* ** *<.001.*

3.4 Modulation by Unpleasant Pictures: Main Effect MDD

The current section depicts the statistical differences for unpleasant pictures regarding the main effect of MDD. Figure 2.4.a shows the main significant clusters from the SPM t-test analysis of the main effect of depression for unpleasant pictures ($t(68) = 2.38$; $p<.01$), where both, right superior parietal cortex and left parietal operculum exhibit a decreased activity for the MDD patients when compared to healthy control subjects.

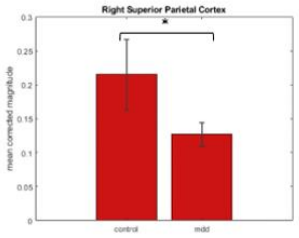
Similarly to the arousal modulation analysis, results show the decreased activity at the right parietal (figure 2.4.c) and the left operculum (figure 2.4.d) in MDD patients compared to healthy control subjects, which consistently with the arousal modulation results supports previous evidence of a parietal decreased excitability in depression (Kayser et al., 2017; Moratti et al., 2015), which could indicate a lower attentional modulation of unpleasant stimuli. Moreover, the right superior parietal cluster overlaps for both arousal and unpleasant condition (figure 2.4.b).

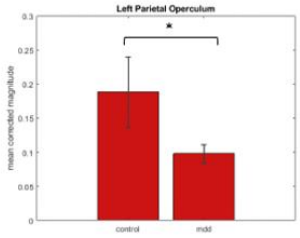
Unlike the MDD factor on arousal modulation analysis, no significant differences came out on frontal regions.



a. SPM t-test agecorrected

b. Topographic comparison
Arousal vs Unpleasant ANCOVAs





c. Right Superior Parietal Cortex

d. Left Parietal Operculum

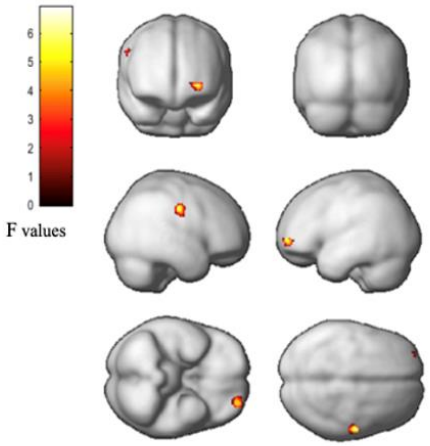
Figure 2.4: SPM t-test contrast between healthy control and depression group in unpleasant modulation (unpleasant - neutral) ssVEF adjusted magnitude including the age of the participants as covariate (t (68) = 2.38; p<.01) (a). t-test unpleasant parietal cluster represented in red shows a partial overlap with the resulting t-test cluster of arousal modulation represented in green (b). Bar plots illustrate the mean and the standard error ssVEF adjusted magnitude of healthy control and depression groups, where the last exhibit decreased activity in the right superior parietal and left central operculum (c-d). *Note: * <.01; ** <.001.*

3.5 Modulation by Pleasant Pictures: Interaction Family History and MDD

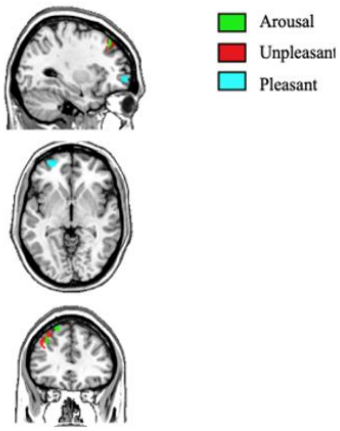
This section collects the statistical differences of the pleasant valence using the neutral condition as a baseline (pleasant - neutral), where figure 2.5.a. shows the significant clusters of the SPM ANCOVA ($F(3.68) = 4.08$; $p<.01$; $k=100$ voxels) of family history of depression and major depressive disorder concerning the ssVEF modulation under pleasant stimulation only, distributed across the right postcentral gyrus (figure 2.5.c) and the left middle frontal gyrus (figure 2.5.d).

Figure 2.5.b shows how FH+ exhibit a reduced ssVEF amplitude independently of current depression status at right postcentral gyrus ($t(75) = 3.57$; $p < .001$). Moreover, no significant differences appear regarding current depression status within FH- ($t(41) = 1.77$; $p = .083$) and FH+ ($t(32) = 1.02$; $p = .313$) groups in this region.

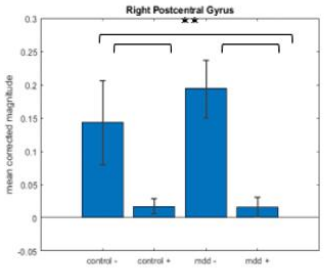
Unlike right postcentral gyrus, this difference is marginally significant only within the control group at the left middle frontal gyrus ($t(34) = 2.00$; $p = .053$), where FH+ exhibit a decreased ssVEF amplitude when compared to FH- (figure 2.5.d). No differences appear within the MDD group in this cluster ($t(32) = .66$; $p = .510$).



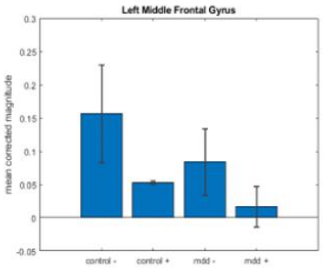
a. SPM t-test agecorrected



b. Topographic comparison Pleasant vs Arousal vs Unpleasant ANCOVAs



c. Right Postcentral Gyrus



c. Left Middle Frontal Gyrus

FIGURE 2.5: SPM ANCOVA pleasant modulation (pleasant - neutral) ssVEF adjusted amplitude including the age of the participants as covariate (F (3.68) = 4.08; p<.01; k=100 voxels) (from left to right: Control | FH-; Control | FH+; MDD | FH-; MDD | FH+). (a) represented in blue (b) shows no overlap within left and right middle frontal gyrus across resulting clusters from unpleasant and arousal modulation SPM ANCOVAs represented in red and green respectively (b). Bar plots illustrate the mean and the standard error values of the ssVEF adjusted amplitude of each experimental group regarding to the main factors *depression* and *family history of depression* for each significant cluster resulting from the ANCOVA interaction analysis (c and d). Note that, while ssVEF adjusted amplitude exhibit decreased values for both healthy and depression FH+ at right postcentral gyrus, this difference is significant only within non-depressed group in the left middle frontal gyrus. *Note: * <.01; ** <.001.*

4 Discussion

4.1 Arousal modulation

Our results show an interaction between the depression status and the family history with respect to ssVEF amplitude modulation by arousal, where the factor family history of depression exhibits differences only within healthy control subjects but not within the depression group: Results show increased ssVEF amplitudes in the right parietal cortex and left middle frontal gyrus for the FH+ control group when compared to FH- controls, while the ssVEF arousal modulation in the right middle frontal gyrus is lower in the FH+ controls compared to the FH- healthy participants.

Regarding this unexpected unbalance between the right parietal and the right frontal in healthy FH- subjects, we tested the correlation between both regions. However, despite the negative tendency ($r = -0.334$) the correlation analysis between the right parietal and the right frontal cortices shed no significant values ($p = .174$) (figure 2.1.3.a). The lack of significance within the correlation could be due to the low number of observations (18 subjects) within this condition. However, study of the unbalanced relationship between these regions regarding the family history of depression should be considered for future experimental designs.

Given previously findings of the impact of high levels of anxiety on the right parietal cortex in the arousal modulation performance (Heller, 1997and 2003; Mcnamara et al., 2016; Kayser et al., 2017), which can lead to enhanced activity modulation in this region, the same SPM ANCOVA analysis was performed introducing the individual levels of anxiety (HARS scores) as a covariate: No differences appeared when compared to the first age-corrected SPM ANCOVA, indicating that, importantly, the analysis of the variance cannot be explained by the effect of the anxiety (figure 2.1.1.b of results)

Regarding the family load of depression within the MDD group, the ANCOVA reports no significant differences: Attending to the bar plots (figures 2.2.) and based on the significant differences of the main effect of depression on ssVEF arousal modulation

amplitude (figure 2.1 and 2.2), which consistently with previous evidence points to an impaired fronto-parietal attentional network performance in current MDD status (see introduction section 1.3), the lack of significant differences within this group regarding the FH factor would be explained by a systematic failure in the fronto-parietal network in the current depression, masking therefore the effect of the FH on the depressed population.

Critically, regions indicated by the ANCOVA and the t-test for the main effect of depression do not overlap (figure 2.1.b), allowing the isolated interpretation of the main effect results of MDD. However, as most of the MDD population was under antidepressant drug treatment, it is worth contemplating that this effect could also be masking the eventual differences in FH within the MDD group.

The main effect of MDD shows three significant clusters where MDD patients exhibit lower ssVEF amplitude modulations by emotion compared to the healthy control group. Consistent with previous reports (Kayser, 2000; Kayser et al., 2017; Moratti et al., 2008), our results show a lack of modulation in the superior parietal and the right middle frontal cortex (section 1.3 results), previously characterize in the attentional network (Bradley, 2010). However, we cannot interpret the cluster shown in the left operculum as we did not have any hypothesis with respect to this brain region. However, the emerging result should be taken into consideration for further research.

4.2 Modulation by Unpleasant Pictures

Section 2.1 depicts the results of the normalized unpleasant condition (unpleasant – neutral). The SPM age-corrected ANCOVA (figure 2.3.a), shows a similar tendency to the arousal modulation analysis: enhanced ssVEF amplitude modulations in the right pre and post-central and the left middle frontal gyrus, while the ssVEF modulation was reduced in the right middle frontal gyrus. Aligned to the arousal modulation, these differences were observed only in the control group (figure 2.3.a-c-d-e-f). Consistently with the results obtained in the ANCOVA analysis for the arousal modulation, the absence of significant differences within the depressed group under unpleasant stimulation supports the idea of a

masked effect of the FH factor by the MDD itself on the emotional fronto-parietal processing.

Regarding the two-samples SPM t-test of the main effect of MDD, two significant clusters emerge at the right parietal and the left operculum, where both exhibit reduced ssVEF amplitudes modulated by unpleasant for the MDD group compared to the control group. Interestingly, unlike the ANCOVAs results for unpleasant and arousal modulation, here the effects at the right parietal cortex overlap in both arousal and unpleasant ssVEF modulations. Moreover, the unpleasant cluster is bigger (k = 553 voxels size) than the arousal cluster (k = 172 voxels size), inviting to consider whether the unpleasant ssVEF processing can be leading the arousal main effect of MDD.

On the other hand, unlike the arousal modulation, no significant differences appeared in any frontal or anterior cortical region, suggesting again that, even when the parietal arousal modulation seems to be driven by the unpleasant images, the responsible network for each process would be different. *As mentioned in the previous section, due to the lack of anticipation of the role of the left operculum in the hypothesis, the role of this region on unpleasant processing will be explored in further research.

4.3 Modulation by Pleasant Pictures

Section 3 of the results reports on the differences across experimental groups for the normalized pleasant condition (pleasant – neutral). As illustrated in figure 2.5.a, two significant clusters appear at the right pre-central and the left middle frontal.

Interestingly, unlike the previous ANCOVA results for unpleasant and arousal modulation, here the right postcentral gyrus exhibits a decreased response to pleasant pictures for the FH+ individuals for both, MDD patients and healthy controls. Importantly, these results suggest that the differences in emotional processing in this region do not rely on the current status of MDD but on the familial load of MDD (figure 2.5.c).

Further, the SPM ANCOVA shows a different tendency for the left middle frontal gyrus (figure 2.5.d), where the post hoc t-test reveals significant differences regarding the family history only in the healthy control group. Interestingly, as it can be appreciated in figure 3.1.b, ssVEF modulation for normalized pleasant pictures, do not overlap with the unpleasant nor with the arousal modulation. Moreover, the resulting left frontal ssVEF modulation exhibits an opposed activation pattern at the left frontal cortex under pleasant modulation when compared to both arousal and unpleasant conditions.

Previous evidence has pointed to the preponderant role of the left frontal activation in current MDD status while the right posterior activation is more related to the predisposition to suffer from depression (Robinson and Shimoda, 1999): Our results suggest that not only the right parietal but the left frontal cortex is involved in the predisposition to suffer from MDD, which also exhibits opposed amplitude patterns as a function of the valence of the presented pictures. On the other hand, opposed to Robinson and Shimoda (1999), the post hoc analyses show no significant differences regarding the current depressed status in this region.

The fact that relative left enhanced frontal activity in emotional processing has been related with a higher positive mood (Heller, 1997) and latter interpreted as a signature of approach tendency in healthy subjects (Davidson, 2003; Harmon-Jones et al., 2010), leads to interpret the current down-modulated ssVEF amplitude for pleasant pictures in the left frontal region for healthy participants with family history of depression as the signature of an impaired tendency in the approaching behaviors to pleasant emotional stimuli.

1 Introduction

1.1 Neural Principles of cardiac activity

Cardiac activity has been a capital tool for diagnosis in the medical field. However, it was not until the beginning of the XIX century that it became a subject of interest in the field of psychophysiology.

Compared to the galvanic response, the heart is innervated by both the sympathetic and parasympathetic branches of the autonomic nervous systems, rendering it a helpful tool that provides complex information about the autonomic nervous system functioning (Carretié, 2009).

a. Sympathetic innervation:

Responsible for the cardiac tissue stimulation and hence, the increment of the heart rate frequency, the sympathetic branch of the cardiac system comprehends outputs from the CNS (Central Nervous System); concretely from the brain stem and the diencephalon, including regions in the medulla, pons, and hypothalamus that projects to the spinal cord. Five central brain regions have been identified in the innervation at all levels of sympathetic outflow: the paraventricular hypothalamic nucleus, A5 noradrenergic cell group, caudal raphe region, and ventromedial medulla (Fundamental neuroscience). Although the noradrenalin from the suprarenal path and all catecholamine cells from the brainstem, the principal neurotransmitter of the sympathetic preganglionar synapses is glutamate.

b. Parasympathetic innervation:

Responsible for the heart rate decrease and therefore for the relaxing cardiac periods, the cardiac preganglionic parasympathetic neurons resident in the nucleus ambiguus of the ventrolateral medullary reticular formation and the dorsal motor nucleus of the vagus nerve barely innervate the parasympathetic cardiac response. Although dorsal motor nucleus and nucleus ambiguous neurons are phenotypically cholinergic, some cardioinhibitory neurons

in the nucleus ambiguous are under GABAergic inhibitory control (Fundamental neuroscience).

In addition to the preganglionar and peripheral structures responsible for the cardiac rhythm modulation, several structures are involved in the cardiac tissue for the correct performance of the cardiac rhythm. We could divide the cardiac period into five main steps, each responsible for a specific anatomical response of the heart and lead by a specific cardiac structure:

1. The cardiac contractions are led by the nodal tissue, constituted by a special kind of muscular fibers capable of producing action potentials without neuronal innervation. This tissue is located in the right atrium and is composed of the sinoatrial node (SA) and the atrioventricular node (AV): while the first set the pace and tempo of the cardiac response, the second spreads the action potentials through the Purkinje System.

2. The auricular contraction begins with the action potentials originated in the SA, leading to the auricular systole.

3. During the auricular diastole, the nodular action potentials reach the AV, spreading the potentials across the Bundle of Hiss. This one is itself divided into the Left and Right Bundle Branches, encompassing both ventricles and triggering the simultaneous systole of both ventricles. This nodular framework composes the Purkinje System, responsible for the accurate spread of the potentials across the cardiac tissue.

4. The SA is innervated by neurons led by the medulla oblongata in the brain stem. Therefore, its activation results in increased heart rate known as tachycardia. The sympathetic system also stimulates this increment of the heart rate frequency by the segregation of adrenalin from the suprarenal medulla.

5. On the other hand, both SA and AV are barely innervated by parasympathetic preganglionar cells from the tenth cranial pair nerve (vagus) led by the dorsal vagal nuclei of the medulla oblongata. It is, therefore, responsible for the heart rate reduction

or bradycardia, decreasing the spontaneous depolarization rate by segregating acetylcholine (Larsen et al., 1986; Browley et al., 2000).

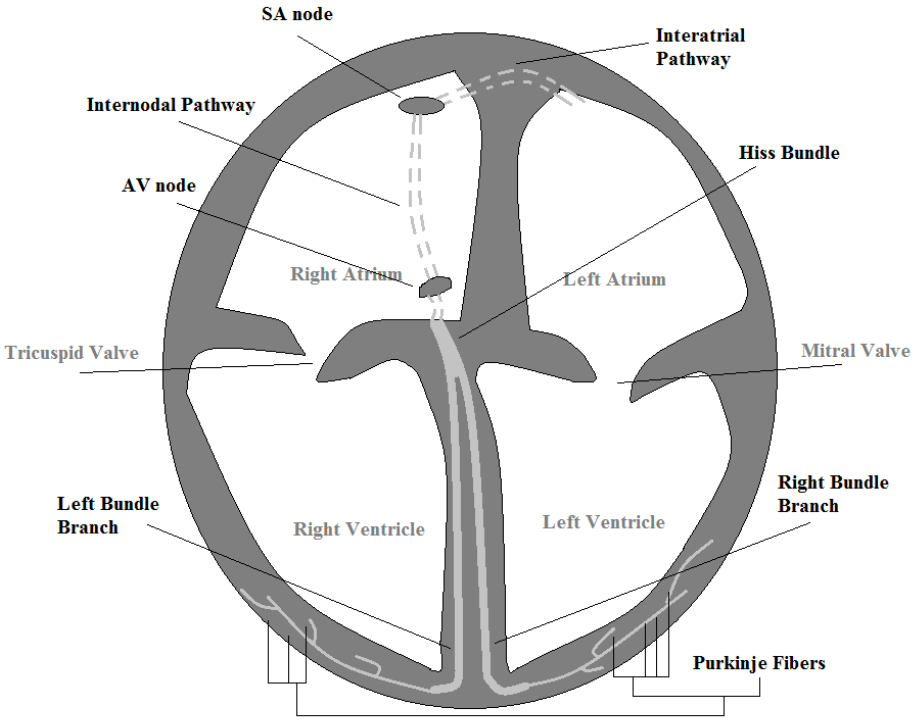


Figure 3.1. Schematic representation of heart and its principle neural structures.

1.2 Cardiac activity measures: The electrocardiogram (ECG)

The relatively electrical solid activity required for the cardiac contraction (≈2mV) makes it a relatively straightforward measure (carretié, 2009). This leads to the cardiac noise we find as artifact in the electroencephalogram and magnetoencephalogram that requires specific filtering to avoid the impact of this activity in the recordings, as discussed in the methods section.

To measure the cardiac response (ECG), only three sensors are required (of course, in clinical settings, more complicated montages can be applied): two bipolar sensors and one ground electrode. The bipolar sensors, responsible for the direct measure of cardiac activity, are usually located on each arm. This distribution can be problematic due to the noise from arm and hand movement, especially when the task demands motor response. To avoid this noise source, polar electrodes can be located one on the left clavicle bone and the other on the last right riff (Carretié, 2009). The ground sensor should be located in a non-muscular activity region like the tip of the nose or ear lobe (Carretié, 2009).

According to the activity of the previously described functional regions, we can decompose the ECG signal in four main components of the cardiac cycle in sequential order:

1. *P wave*: is the first component we find in the cardiac signal wave and falls to the depolarization of the auricular nodular fibers, hence reflecting the auricular systole. This first component spouse the trigger of the whole cardiac cycle.

2. Q-R-S complex: the complex corresponds to the Purkinje system activity and, therefore, to the ventricular systole. During the ventricular contraction, the auricular diastole repolarization takes place. Nevertheless, due to the different power potential, this second event results masked by the previous one. This event is composed of three main waves:

a. *Q wave*: leading the Q-R-S complex, represents the depolarization of the interventricular septum

b. *R wave*: known as *R-Peak*, represents the most salient event of the cardiac cycle in the ECG as it reflects the early ventricular depolarization.

c. *S wave*: closing the *QRS event* represents the depolarization of the Purkinje fibers

3. *T wave*: is the last event we find in the cardiac cycle and appear some milliseconds after the QRS complex. The T wave reflexes the repolarization of Purkinje System during the ventricular diastole a therefore, the refractory moment of the system.

4. Respiratory sinus arrhythmia: We can appreciate a fluctuation in the rhythm of cardiac cycles or heart rate by analyzing the distance between cardiac cycles. This normal fluctuation corresponds to the inhale (heart rate increase: tachycardia) and to the exhale (heart rate decrease: bradycardia), respectively.

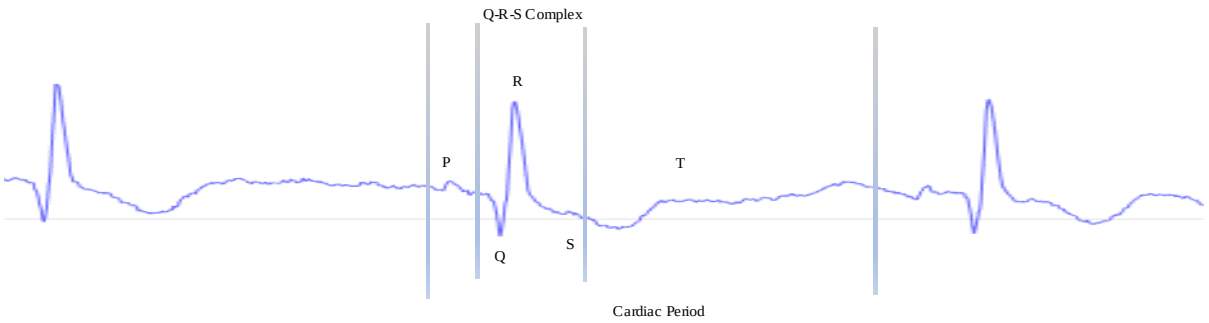


Figure 3.2. Representation of the Cardiac Period taken from original ECG from one subject trial, visualized with Bainstorm.

1.3 ECG Signal Analysis

Due to the characteristic innervations and relationship between the heart and autonomous nervous system, cardiac activity analysis has resulted in a robust method in studying psychophysiological processes across the last century.

To analyze the subjacent autonomous activity, the analysis of cardiac activity focuses on the heart's pumping rate: heart rate change. Specifically, on the changes in this rate's latency, resulting in a higher rate when sympathetic activity is predominant and lower when parasympathetic activity.

To estimate these changes and get a rate of the heart contractions, we reference the R peaks and calculate the distance between them (inter-beat-intervals) in the time domain (Carretié, 2009). This measure can be transformed into beats per minute (bpm), being around 70 bpms during resting-state recording, but varying across subjects. The low resolution in terms of time makes it necessary to take relatively long periods of recording time (from 4 seconds on) and baseline to get coherent results (Acharya et al., 2006)

As previously mentioned, when we analyze the cardiac activity in terms of heart rate, we analyze both sympathetic and parasympathetic activity together. Nonetheless, there are specific parameters to analyze the isolated activity of both systems:

Sympathetic activity: we can get access to the isolated activity of this system estimating the amplitude of the T wave. The T wave reflects the ventricular repolarization before the R peak amplitude during the refractory moment, portraying the sympathetic activity exclusively.

Parasympathetic activity: A usual tool to estimate the isolated parasympathetic activity is based on the analysis of the respiratory sinus arrhythmia. We can get access to it by the spectral analysis of heart rate, concretely, on the low-frequency band (between .15 and .40 HZ). The result of this analysis represents the joint vagus parasympathetic innervation of both lungs and heart.

Attending to the aim of the study, we find two main approaches in the heart rate analysis: heart rate change and heart rate variability. While the first one focuses more on the discrete response to a specific stimulus, the second focuses more on the heart rate variability across longer periods of time. Therefore, the heart rate change has been deeper studied on fast specific responses on the field of emotion and attention (from 3 to 6 seconds) (Lacey and Lacey 1973, Bradley 2009., 2007, Lang et al., 2012; Moratti et al, 2004, Lang, Simons and Balaban, 2011), while heart rate variability has been related to the study with chronic diseases and longer resting-state recording time periods (from 5 minutes to 24 hours) (Acharya et al., 2006). However, previous studies have related resting state HRV with HR change to specific sues (Cacioppo et al., 1994).

1.4 HR and Emotions: Orienting Response

The orienting response has been studied as a paradigmatic reaction of the human being in psychology that involves perceptual, attentional, and emotional processing, among others. The Orienting response (OR) was first described by Ivan Pavlov in 1927 and defined under the name of Orienting Reflex as a set of reactions evoked in an organism by a novel stimulus manifested by an interruption of the ongoing activity accompanied by turning eyes, head, and body movement subjectively experienced as an involuntary switch of attention (Konorski, 1948).

Later, Sokolov (1960) introduced the role of the autonomic response in the orienting reflex in which learning and perceptual processes have a significant effect (Sokolov, 1960). Thereby increased sympathetic activity would have an excitatory and facilitating effect in order to evoke or maintain cortical activation (graham et al., 1996). According to Sokolov, this accelerative process would appear in three primary responses: defense, adaptation, and orienting, where the last one comprehends a set of unconditioned motor, autonomic and central responses elicited by any change in stimulation, independent of stimulus quality (Sokolov, 1960).

On the other hand, Lacey and Lacey (1973) argue that the heart rate increase would be associated with a reduction in sensitivity to stimulation, facilitating the "rejection of the environment" and are expected to occur in painfully or unpleasant contexts and those where external distracters would interfere with the internal processing. In addition, heart rate decrease would correlate with increased attention and sensitivity to stimulation (Lacey & Lacey 1973), and therefore, we would expect a heart rate deceleration during the orientation response.

The first authors pointing out the heart rate reaction to stimuli as an attempt to characterize the HR within the OR, was Davis, Buchwald, and Frankmann (1955), who analyzed the first 20 beats after stimulus onset (white noise), identifying a diphasic response whereby HR initially increases before a deceleration within the next 5 seconds after post-stimulus onset. Two years after, Davis and Buchwald replicated the results using images (Davis and Buchwald, 1957).

In the early '90s, Bradley conceptualized OR as "a set of functional responses, with different rates of habituation, that index specific central, perceptual, and motor processes" (Bradley, 2009). Bradley claimed for an integrative model of attention and emotion. To this end, she used emotional relevant visual stimuli taken from the International Affective Picture System (IAPS) (Lang, Bradley and Cuthbert, 1997) as a tool to elicit positive, neutral and negative emotions and validate the visceral reaction in terms of electrodermal response, heart rate change, pupil diameter and EEG (Bradley, 2010). In this exhaustive study of the central and autonomous response to emotional stimuli, Bradley also points out an attenuated cardiac response in terms of deceleration when stimuli are repeated, denying Sokolov's idea about orienting and adaptation response behaving the same way. In opposition to Sokolov, she pointed out that while HR deceleration is related to OR, the accelerative response corresponds to defense system activation (Sokolov, 1960). Hence, they both response types being different processes (Bradley neural selective). She also adds this cardiac deceleration to the OR while previous analysis from Graham labeled this brief decelerative response as a "transient detecting response" (TDS) and did not consider it to be a component of the cardiac OR (Graham, 1987).

Attending to the differences across conditions, Bradley points out a systematic larger deceleration for the unpleasant stimuli compared to neutral and pleasant ones, suggesting an enhanced sensory processing with a pronounced perceptual focus for these aversive cues (Bradley, 2009).

Taken together, Bradley proposes a Motivational Model of Emotion where the stimulus significance in terms of pleasure and arousal provides the first link between emotion and orienting (Bradley, 2009)

As far as cardiovascular changes reflect metabolic adjustments to environmental demands (Palomba et al., 1997), the cardiac activity analysis, together with EEG, EOG, or galvanic responses, has been widely used to study cognitive and affective processes associated with the orienting response (Lacey and Lacey, 1974; Palomba et al., 1997; Moratti et al., 2004; Lang, Simons and Balaban, 2011; Bradley., 2009). Thereby, stimulus-evoked HR changes have been mostly utilized to characterize the modulation of the OR and defense system activation, respectively.

1.5 HR and Depression

Cardiac activity has been widely studied in MDD as a signature of the autonomous affectation in patients suffering from MDD. Even when there is not a firm agreement about the cardiac reactivity in MDD patients due to the contradictory results, most of the studies in this topic describe a blunted cardiac response estimated on HRV frequency in MDD patients compared to those without MDD symptoms (see meta-analysis Kemp et al., 2010; Anna C Phillips 2010; Solomon et al., 2013; J.Zhu et al., 2019).

Due to the significantly higher prevalence of cardiovascular diseases (CVD) among MDD patients, the relationship between both pathologies has been studied analyzing the HRV during resting state periods (Malzberg, 1930). Different studies have shed light on the relationship between MDD and CVD, pointing to greater autonomic dysfunction and indicating a significantly lower modulation of cardiac vagal tone in patients reflected by a decreased HRV (Agelink et al., 2002). Carney et al. (2009) focused on the cardiac response

if individuals with and without MDD superimposed with stable coronary disease or a recent acute coronary event, finding a lower HRV for depressed patients, concluding the critical role that decreased HRV could be playing as a risk factor of coronary disease in MDD patients (Cartney et al., 2009).

Moreover, it has been suggested that the underlying autonomic dysfunction associated with MDD could be a linking mechanism between depression and the high cardiac mortality of MDD patients (Carney et al., 2009), is actually reported as a predictor of cardiovascular events (Leroy et al., 2010)

In addition, other studies argue that the lower HRV scores in MDD patients may contribute to the elevated risk of CVD of MDD patients claiming for a higher characterization of HRV and autonomic response is needed (Taylor et al., 2010).

On the other hand, it has also being emphasized the high prevalence of non-healthy habits which would increase the probability of CVD such as smoking, fat eating, alcohol drinking, or the lack of exercise usually found in MDD patients, being those behind the CVD rather than autonomic dysfunctions per se in this population or at least making impossible to isolate the impact of both phenomena (Taylor et al., 2010).

The origin of these HRV differences and its possible relationship with the pharmacological treatment of MDD still controversial: while it seems to be quite clear the decreasing HRV measures effect of the tricyclic antidepressants (Davidson et al. 2005), there is not a strong covenant within the selective serotonin reuptake inhibitors, due to the evidence supporting that these differences disappear with the SSRI treatment (karpyak et al. 2004), while other studies find no significant evidence of the impact of these treatments in the differences at HRV level among groups (see meta-analysis kemp et al., 2010.). However, the lack of studies supporting this evidence should be emphasized (Tayloret al., 2010).

In addition, changes in cardiac response due to pure psychological treatments without pharmacology such as relaxation therapy and biofeedback have shown an acute but modest effect reducing HR. Cartney et al. (2000) found differences in severe MDD patients after

therapy, while no differences were found in mild depressed and non-depressed individuals. In addition, a positive effect of cognitive-behavior therapy (CBT) decreasing HR was shown by Taylor et al. (Taylor et al., 2009). Unfortunately, the relationship between CBT and HR cannot be isolated from additional changes in life habits, such as exercise or feeding routine (Taylor et al., 2010).

In the study of MDD and HRV, we found a few main approaches: resting-state monitoring and emotional task performance. Attending the first one, Kemp et al. (2010) showed on a meta-analysis based on 18 articles a generalized blunted HRV response in MDD patients compared to healthy individuals. Moreover, they found a negative correlation between HRV and the severity of the symptoms, suggesting a negative correlation between the degree of depression and the autonomous modulation of the cardiac response (see meta-analysis Kemp et al., 2010).

While the resting state HRV has been widely explored, little evidence of cardiac reactivity to stressing laboratory conditions can be found in the literature. Salomon et al. (2009) compared individuals' cardiac response while neutral clip viewing and a stressful task performance such as the speech task, where participants were asked to prepare and declaim a speech. In addition to resting-state studies, the results suggest an attenuated cardiac response to the stressful situation from the MDD patients compared with a control group, supporting the blunted response hypothesis in the MDD (Salomon et al., 2009, Salomon et al., 2013).In the same line but focusing on the frequency domain analysis of the HRV under emotional induction (happiness, sadness, anger, and neutral) before and after pharmacological treatment of MDD patients, Fraguas et al. (2007) found a positive correlation of the antidepressant reaction under sadness induction in the low-frequency band and both, low and high frequency for the happiness condition. Therefore, they suggest the HRV as a candidate for the antidepressant reaction predictor in induced emotion (Fraguas et al., 2007). In addition, in a recent study, Barrione et al. (2018) focused on the impact of melancholic features and the HRV in MDD patients. However, the authors pointed out that due to the nature of their study, it is not possible to know whether depressive symptoms lead to changes in HRV as an index of a dysfunction of the autonomous system, or if the

autonomous dysfunction is the one who trigger the depressive symptoms (Barrione et al., 2018).

1.6 HR and Heritability

Within the frame of the cardiac response as an index of the autonomous response and taking into account the previously mentioned differences across MDD patients compared to non-depressed subjects, the next arising question is whether these differences would or would not be mediated by heritability factors. To date, we can find strong evidence of genetic as a risk factor of MDD, but not many studies have focused on the autonomous response as an index of MDD heritability factor. Nonetheless, Rottenberg (Rottenberg et al., 2005) pointed out the blunted cardiovascular reactivity as a predictor for future depression, being this a reliable predictor of future depression. In other words, blunted cardiovascular reactivity would suggest the risk of suffering eventual future MDD and not necessarily a current depression (Salomon et al., 2013). Under this assumption, it would be reasonable to consider the autonomous and, hence the cardiac response, to be modulated by a genetic background of depression.

1.7 Hypotheses

As the present study aims to analyze the eventual attentional system differences at the peripheral level between healthy subjects and patients with major depressive disorder, we focus on the heart rate change to measure the autonomous response to emotional content stimuli and its eventual differences in the Orienting Response cardiac response.

We hypothesize that depressed patients would exhibit a reduced cardiac and autonomous response to emotional compared to neutral stimuli as a correlate of the anhedonia MDD.

We also hypothesize differences between healthy control individuals and MDD patients' cardiac response to emotional stimuli, revealing a flattered response in MDD patients reflecting a less flexible autonomic response.

Moreover, given the last evidence of differences in cardiac response as a predictor of future depression and therefore, probably modulated by the genetic background of the individuals, we will explore the origin of these differences by comparing those subjects with and without a previous family history of major depression disease as an exploratory sign of the relevance of possible endophenotype of MDD altering the autonomic response of individuals to emotional relevant stimulation.

2 Methods

* Because all the data set had been collected following the same experimental procedure previously described (general introduction) and to avoid redundancies, only relevant cues for the current chapter will be described in the present section.

2.1 Subjects

Eighty-three volunteer participants (61 females, 78 right-handed. Mean age = 25.4; range 18 to 55 years) from the original whole sample (N = 91) participated in the study after giving written informed consent and psychological screening. Forty-eight healthy participants conformed the control group while thirty-five patients diagnosed from unipolar major depressive disorder (see general methods) constituted the experimental MDD group. Those subjects for whom the cardiac signal could not be recorded due to experimental issues, neither extracted from the MEG signal by the Independent Component Analysis, were excluded from the sample for the current study.

2.2 Preprocessing RH change data

The heart rate response was monitored and collected by the ECG channel during MEG recording. Additionally, for those subjects for whom technical problems impaired the heart rate recording (n = 8), the magnetocardiographic (MCG) signal was extracted from the MEG recording by an Independent Component Analysis (ICA-Jade) (Rutledge et al., 2013).

In order to get enough resolution, inter-beat intervals were determined based on R-peak time intervals from 5 s before and 9 s after stimulus onset. Heart rate (HR) in beats per

minute (bpm) in 0.5 s steps were estimated using weighted averages (Reyes and Villa, 1998) as implemented in the Matlab toolbox Kardia (Perakakis et al., 2010). Finally, HR change was calculated for the 6 s post-stimulus interval subtracting a 2 s baseline and averaged for each emotional condition picture content: pleasant, neutral and unpleasant.

2.3 Statistical analysis of HR change

According to previous reports (Sokolov, 1960; Lacey and Lacey, 1973; Bradley, 2009), differences in HR across conditions were tested in three different time windows: (1) initial acceleration [0-2 seconds], (2) HR deceleration [2-4 seconds], and (3) the final acceleration [4-6 seconds].

Each time window was estimated averaging HR values within-subject in .05 s steps for each condition. Mean differences between three conditions and across these time intervals were tested by a one-sample t-test for dependent measures within each experimental group: a) control group, b) MDD patients, c) negative family history of MDD, and d) positive family history of MDD.

The interaction between both factors were tested by a two-ways ANOVA, while the post-hoc main effect differences in HR change waveforms across experimental groups were tested by one-sample t-tests for independent measures and one-way ANOVA for each time window. Therefore, in order to get comparable measures across groups, a corrected curve for each group and condition (unpleasant- neutral and pleasant - neutral) was estimated.

3 Results

The results of the current chapter are presented in three main sections corresponding to the control healthy group, the MDD group, and the differences between them and the FH, collecting the statistical analysis across three time-windows of two seconds each across the 6 seconds of stimulation per trial according to the triphasic model of the cardiac response representing: the initial acceleration [from 0 to 2 seconds], the cardiac deceleration [from 2 to 4 seconds] and the final acceleration [from 4 to 6 seconds] for each group.

3.1 Control group

3.1.1 Control group general response

Current section presents the analysis of the resulting time-course curves for the cardiac activity within the 6 seconds time stimulation per trial across the three main conditions: pleasant, neutral, and unpleasant for the control group, represented in blue, gray and red respectively in the figure 3.3.a. Figure 3.3.b. depicts the bar plot where the averaged group response based on the mean response for each subject within each time window is represented in blue, gray and red corresponding to the pleasant, neutral and unpleasant condition. The standard error is represented by the error bars in black.

Statistical analysis (see table 3.1) reveals no significant differences across conditions for the 1st and the 3rd time window but for the second time window for unpleasant vs. neutral (t (47) = 2.397, p = .020) an unpleasant vs. pleasant (t (47) = 2.655, p = .010). No significant differences were found for the pleasant vs. neutral contrast.

Table 3.1

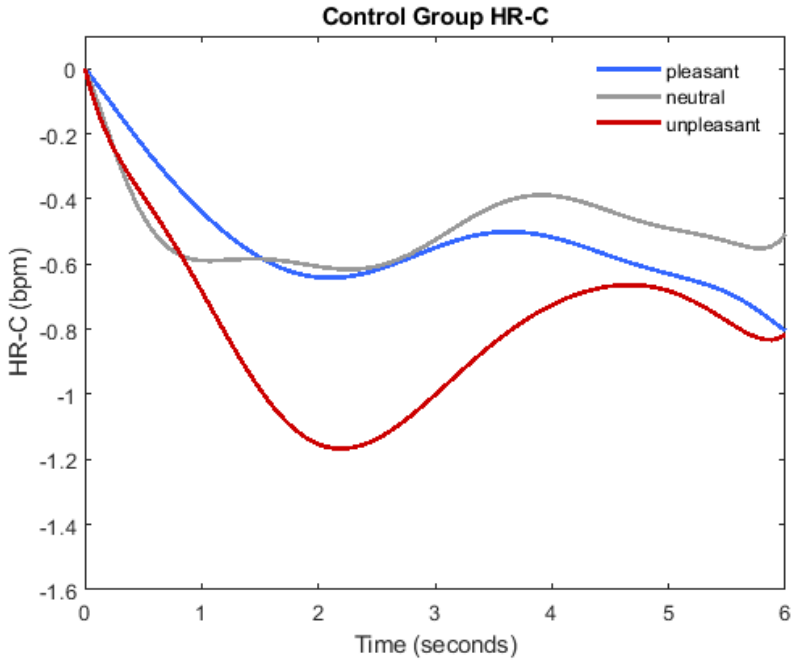
Hear Rate Change: Control Group

	1st time window			2nd time window			3rd time window		
	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant
Pleasant		1.004 (.320)	1.91 (.061)		.111 (0.911)	2.655 (.010)*		.849 (.399)	.550 (.584)
Neutral	1.004 (.320)		.954 (.344)	.111 (0.911)		2.397 (.020)*	.849 (.399)		1.146 (.257)
Unpleasant	1.91 (.061)	.954 (.344)		2.655 (.010)*	2.397 (.020)*		.550 (.584)	1.146 (.257)	

Note. p values noted in brackets. * < .05. DF = 47.

Table 3.1 collects the resulting t-test *t*-values for the statistical analysis of the control group across the three experimental conditions for each time window. The *p*-values are represented inside brackets. The degrees of freedom are not noted and table, being 47 for all the represented t-tests.

a



b

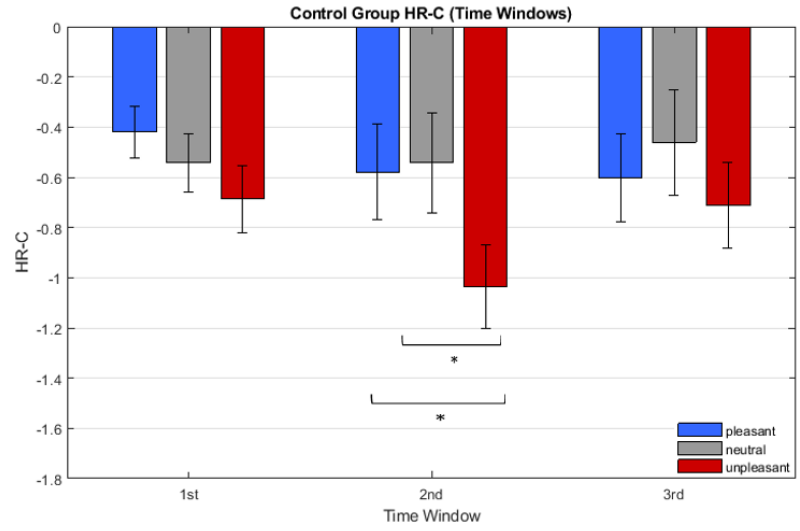


Figure 3.3. represents the heart-rate change response measured in beat per minute of the control group across the three experimental conditions: pleasant (blue), neutral (gray), and unpleasant (red) during the 6 seconds of trial presentation time. a. illustrates the time-course curves based on the group averaged response whereas figure b. illustrates the mean averaged response of the control group for each experimental condition across the three-time windows. The error bar represents the standard error for each condition and time window. *emphasize the significant differences where the p-value is below .05.

3.1.2 Control group subcategorical response

The group response across conditions was estimated based on the resulting averaged response of two subcategories for each condition extracted from the IAPS, where the pleasant condition is composed by erotic and familiar pictures, the neutral condition is conformed by household objects and neutral human faces, and the unpleasant condition is composed by attack and mutilation images. Figure 3.4. depicts the averaged response of the control group for each of these subcategories conforming to the three main experimental conditions, while table 3.2 reports the statistical differences within each category (between subcategories) analyzed in a one-sample t-test.

Results show the significant difference in the unpleasant category within the second time window, highlighting the greater cardiac deceleration between 2 and 4 seconds (corresponding to the orienting response) for the mutilation compared to the attack subcategory. However, we find no significant differences between subcategories in any time window for the pleasant and the neutral categories.

Table 3.2.

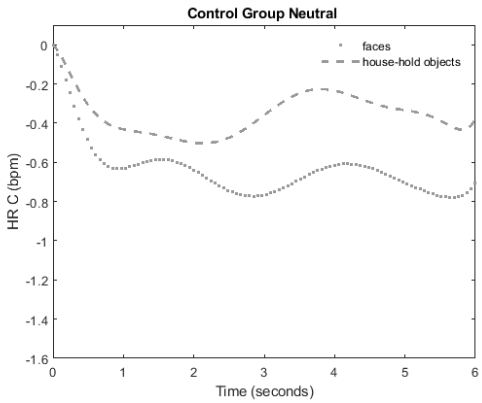
Hear Rate Change: Control Group Sub-Categories

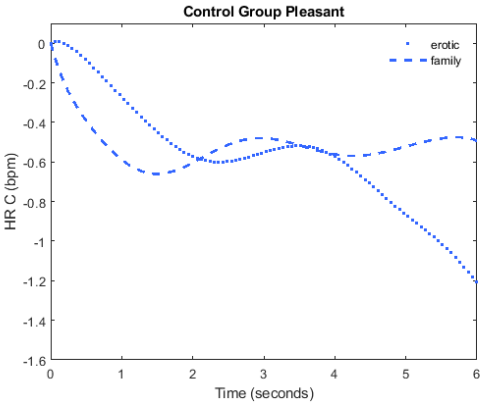
	1st time window			2nd time window			3rd time window		
	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant
Control	1.487 (.143)	.923 (.360)	.866 (.390)	.111 (.911)	1.718 (.092)	2.011 (.050)	.885 (.380)	1.688 (.097)	1.454 (.152)

Note. *p* values noted in brackets. * < .05. DF = 47.

Table 3.2. depicts the statistical outcome from the one-sample t-test between the subcategories within the control group across the three-time windows illustrated in figure 3.3. Pleasant corresponds to Erotica vs. Family; Neutral to neutral faces vs. household objects; and Unpleasant to Attack vs. Mutilation.

a





b

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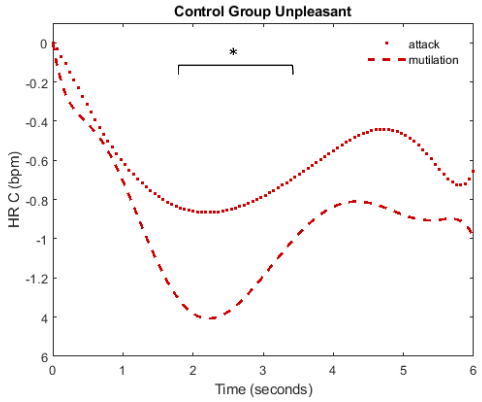


Figure 3.4. illustrates the control heart-rate change group response represented by the time-course curves to each sub-category from the IAPS associated to the belonging experimental condition. Figure 3.4.a represents in gray color the neutral faces (..) and the household objects (--) subcategories conforming the neutral condition. 3.4.b represents the erotic (..) and the family (--) subcategories conforming the pleasant condition. 3.4.c represents the attack (..), and the mutilation (--) subcategories conforming the unpleasant condition. *emphasize the significant differences where the p-value is below .05.

3.1.3 Control group normalized response

In order to obtain comparable measures across experimental groups, unpleasant and pleasant conditions were *normalized* by subtracting neutral condition values to the pleasant and unpleasant condition values respectively. The eventual differences across time windows were tested by one-sample t-test analysis from the resulting corrected curves from the normalized values. Illustrated in figure 3.5, figure 3.5.a shows the normalized pleasant curve response, and figure 3.5.b represents the mean values and the standard errors in the bar plot for each time window, both in blue. Bellow, figure 3.5.c illustrates the normalized unpleasant curve response, while figure 3.5.d represents the mean values and the standard errors in the bar plot for each time window, both in red.

The values from the statistical analysis presented in the table 3.3 revealed no significant differences for the normalized pleasant curve across the three time windows when compared between them. On the other hand, the one-sample t-test analyses reveal significant differences for the normalized unpleasant response for the 2nd vs. 1st time window (t (47) = 2.546; p = .014) and marginally for the 2nd vs. 3rd time window (t (47) = 1.830; p = .053). No significant differences were found between the 1st and the 3rd time window (t (47) = .875; p = .385).

Table 3.3.

Hear Rate Change: Control Group Corrected Curves

	t-test across time windows		
	1st vs. 2nd	2nd vs. 3rd	1st vs 3rd
Pleasant – Neutral	.936 (.353)	.708 (.481)	1.659 (.103)
Unpleasant – Neutral	2.233 (.030)*	1.830 (.053)*	.875 (.385)

Note. p values noted in brackets. * < .05. DF = 47.

Table 3.3. depicts the statistical outcome from the one-sample t-test between the different time windows of the corrected pleasant (pleasant - neutral) and unpleasant (unpleasant – neutral) curves.

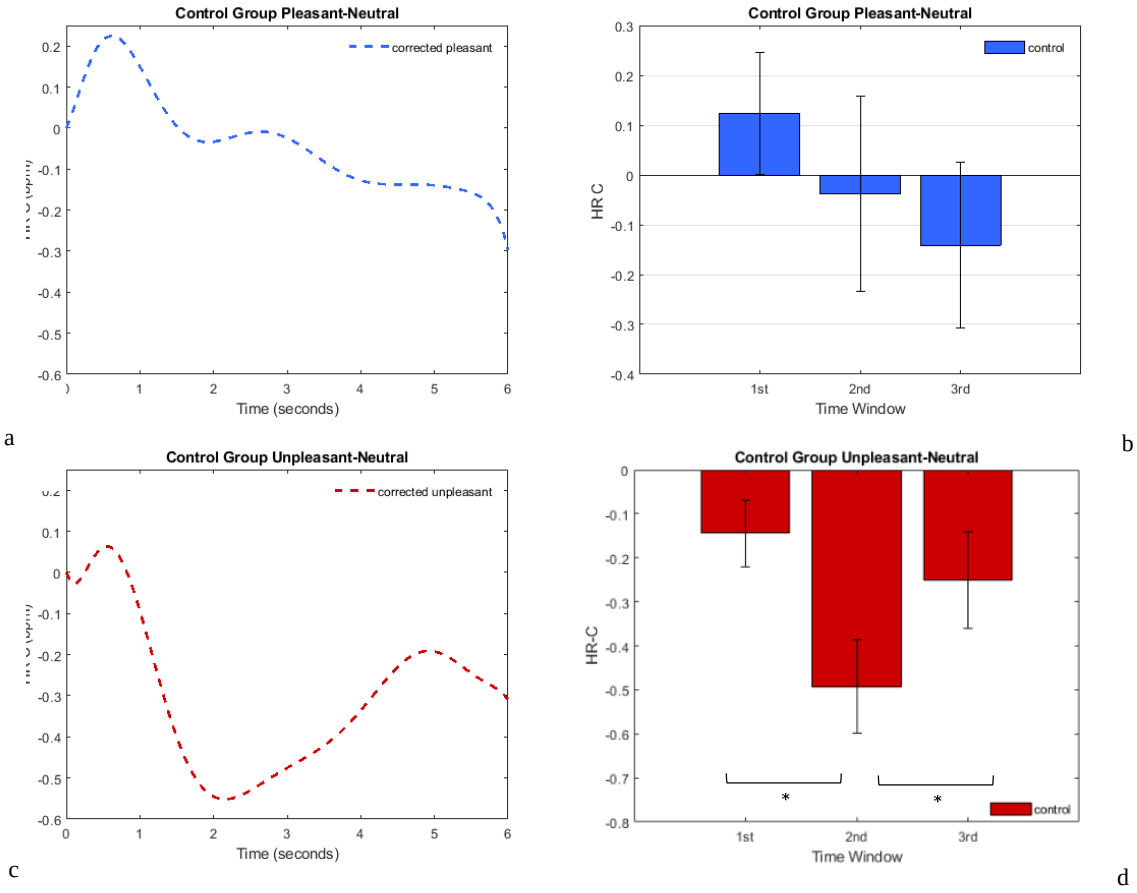


Figure 3.5. Figure 3.5 (*a* and *b*) depicts the resulting curves from the normalized pleasant (pleasant-neutral) and unpleasant (unpleasant-neutral) response in blue and red respectively. Figures 3.5.b and 3.5.d illustrates the mean and the standard error from the normalized pleasant and unpleasant condition represented in blue and red respectively.

3.2 MDD group

3.2.1 MDD group general response

Similar to the previous section, this branch shows the results from the statistical analysis of the time-course response curves of the MDD group across the three main experimental conditions (pleasant, neutral, and unpleasant) depicted in the figure 3.6.a. Bellow, figure 3.6.b. shows the bar plot where the averaged group response based on the mean response for each subject within each time window is represented again in blue, gray and red corresponding to the pleasant, neutral and unpleasant condition. Likely in figure 3.6.b, standard errors are represented by black error bars.

At the statistical level, table 3.4 shows the lack of significant differences for the 1st and the 3rd time windows. However, it is worth mentioning that differences between unpleasant and pleasant (t (34) = 1.966, p = .057) and unpleasant and neutral (t (34) = 1.968, p = .057) during the firs time window, show marginal significance. Unlike, second time window analysis reveals the significant difference of pleasant vs. unpleasant condition (t (34) = 2.107, p = .042) and no significant differences across the resting conditions.

Table 3.4.

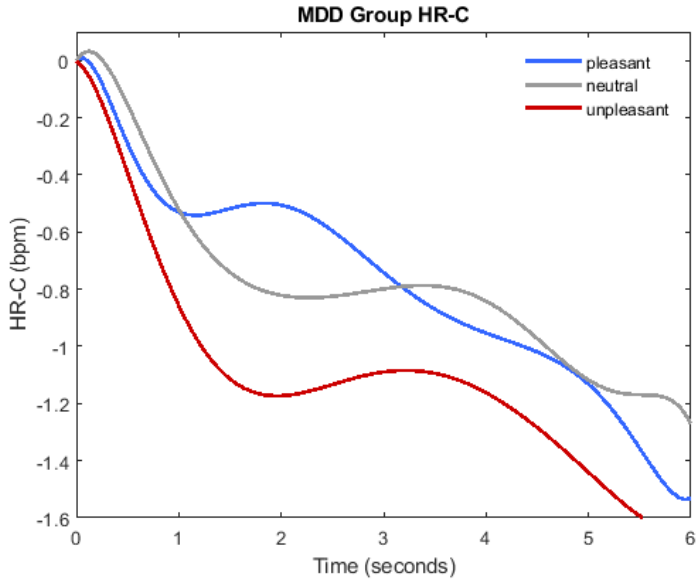
Hear Rate Change: MDD Group

	1st time window			2nd time window			3rd time window		
	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant
Pleasant		.225 (.823)	1.966 (.057)		.921 (.363)	2.107 (.042)*		.471 (.640)	.843 (.404)
Neutral	.225 (.823)		1.968 (.057)	.921 (.363)		1.298 (.203)	.471 (.640)		1.0157 (.255)
Unpleasant	1.968 (.057)	1.966 (.057)		2.107 (.042)*	1.298 (.203)		.843 (.404)	1.157 (.255)	

Note. p values noted in brackets. * < .05. DF = 34.

Table 3.4 collects the resulting t-test *t*-values for the statistical analysis on the MDD group across the three experimental conditions for each time window. The *p*-values are represented inside brackets. The degrees of freedom are not noted and table, being 34 for all the represented t-tests.

a



b

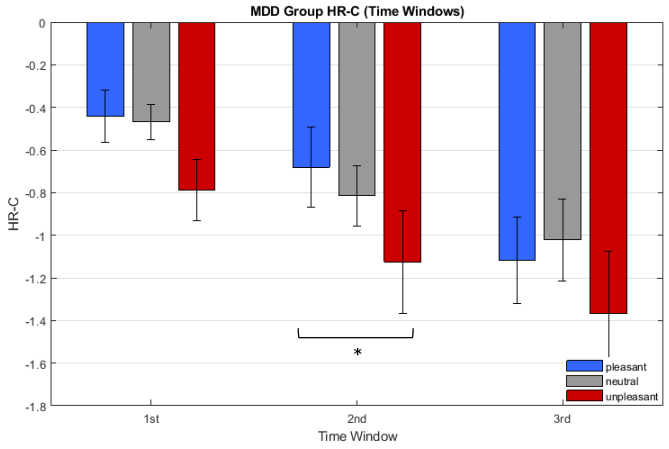


Figure 3.6. represents the heart-rate change response measured in beat per minute of the MDD group across the three experimental conditions: pleasant (blue), neutral (gray) and unpleasant (red) during the 6 seconds of trial presentation time. Figure 3.6.a. illustrates the time-curse curves based on the group averaged response whereas figure 3.6.b. illustrates the mean averaged response of the MDD group for each experimental condition across the three-time windows. The error bar represents the standard error for each condition and time window. * Emphasize the significant differences where p-value is below .05.

3.2.2 MDD group subcategorical response

Alike the control group response specified in section 3.1.2, the group response across conditions for the MDD group was estimated based on the resulting averaged response of two subcategories for each condition extracted from the IAPS, where the pleasant condition is composed by erotic and familiar pictures, the neutral condition is conformed by household objects and neutral human faces, and the unpleasant condition is composed by attack and mutilation images. Figure 3.7. depicts the averaged response of the control group for each of these subcategories conforming the three main experimental conditions.

The resulting values from the one-sample t-test analyses presented illustrated in table 3.5 reveal no significant differences across the three-time windows for any experimental condition in the comparison of its respective composing subcategories.

Table 3.5.

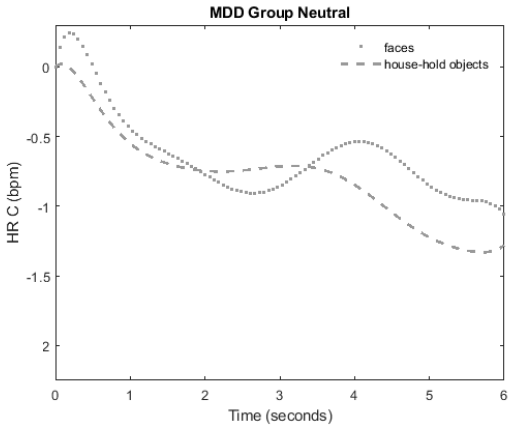
Hear Rate Change: MDD Group Sub-Categories

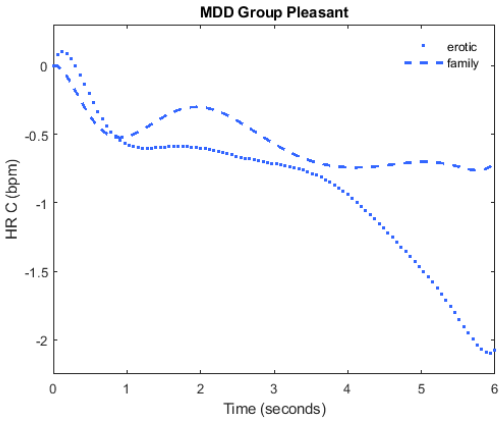
	1st time window			2nd time window			3rd time window		
	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant
MDD	.133 (.894)	.694 (.492)	.019 (.984)	.575 (.568)	.258 (.797)	1.120 (.270)	2.005 (.053)	1.421 (.164)	1.646 (.109)

Note. *p* values noted in brackets. * < .05. DF = 34.

Table 3.5. depicts the statistical outcome from the one-sample t-test between the subcategories within the MDD group across the three-time windows illustrated in figure 2.2. Pleasant corresponds to Erotica vs. Family; Neutral to neutral faces vs. household objects; and Unpleasant to Attack vs. Mutilation.

a





b

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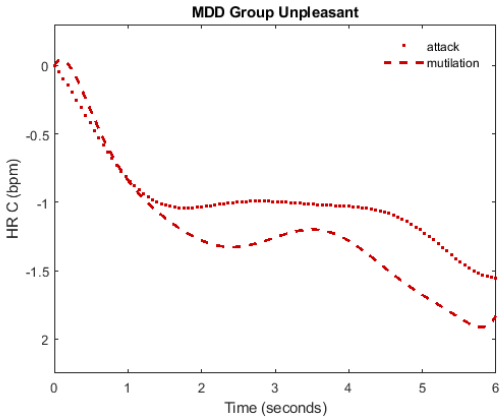


Figure 3.7. illustrates the MDD heart-rate change group response represented by the time-course curves to each sub-category from the IAPS associated to the belonging experimental condition. Figure 3.7.a represents in gray color the neutral faces (..) and the household objects (--) subcategories conforming the neutral condition. 3.7.b represents the erotic (..) and the family (--) subcategories conforming the pleasant condition. 3.7.c represents the attack (..) and the mutilation (--) subcategories conforming the unpleasant condition.

3.2.3 MDD group normalized response

As described in section 3.1.3., in order to obtain comparable measures across experimental groups, unpleasant and pleasant conditions were *normalized* by subtracting neutral condition to the pleasant and unpleasant condition. The eventual differences across time windows were tested by one-sample t-test analysis from the resulting corrected curves from the normalized curve. Illustrated in figure 3.8, figure 3.8.a shows the normalized pleasant curve response and figure 3.8.b represents the mean values and the standard errors in the bar plot for each time window, both in blue. Bellow, figure 3.8.c illustrates the normalized unpleasant curve response, and figure 3.8.d represents the mean values and the standard errors in the bar plot for each time window, both in red.

The statistical analysis illustrated in table 3.6, reveal no significant differences for the normalized pleasant nor unpleasant curves across the three time windows when compared between them.

Table 3.6.

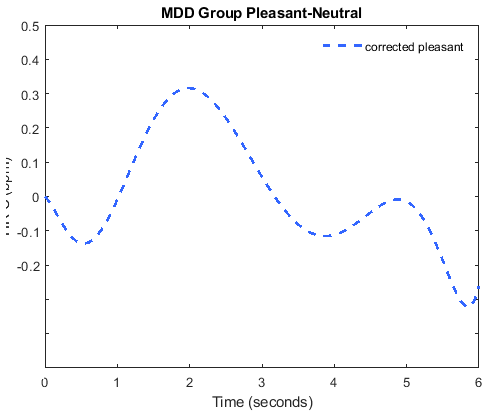
Hear Rate Change: MDD Group Corrected Curves

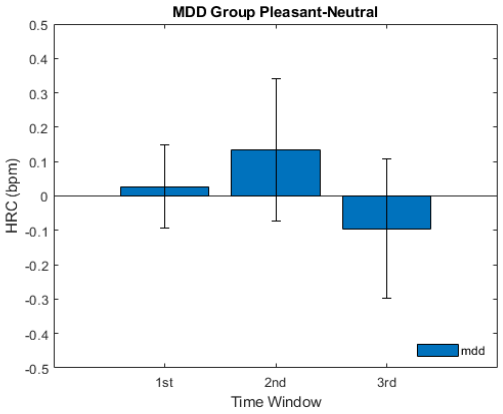
	t-test across time windows		
	1st vs. 2nd	2nd vs. 3rd	1st vs 3rd
Pleasant – Neutral	.610 (.545)	1.254 (.218)	.528 (.600)
Unpleasant – Neutral	.048 (.961)	.141 (.888)	.110 (.912)

Note. *p* values noted in brackets. * < .05. DF = 34.

Table 3.6. depicts the statistical outcome from the one-sample t-test between the different time windows of the corrected pleasant (pleasant - neutral) and unpleasant (unpleasant – neutral) curves.

a





b

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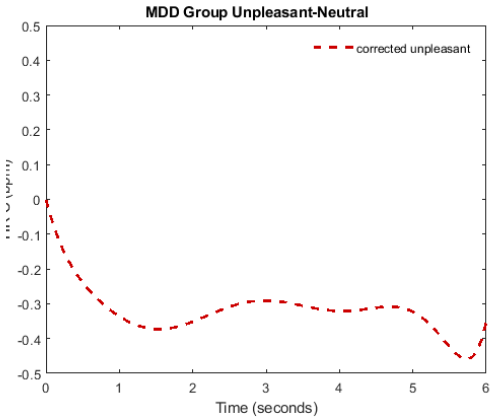
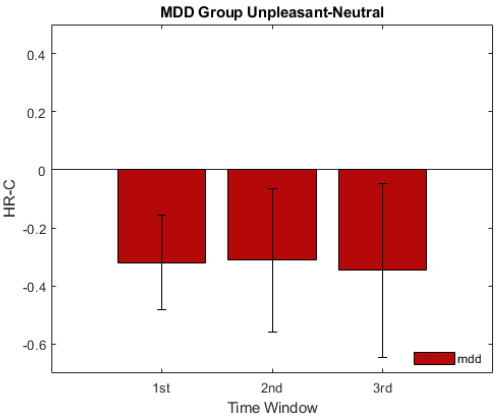




d

Figure 3.8.a and figure 3.8.c depicts the resulting curves from the normalized pleasant (pleasant-neutral) and unpleasant (unpleasant-neutral) response in blue and red respectively. Figures 3.8.b and 3.8.d illustrates the mean and the standard error from the normalized pleasant and unpleasant condition represented in blue and red respectively.

3.3 Major Depressive Disorder and Family History of depression

As previously mentioned, to get comparable measurements across experimental groups (healthy controls and depressed individuals), the obtained measurements for the pleasant and unpleasant conditions were normalized by subtracting the neutral condition values from the experimental ones. This way, the eventual dispersion of the data derived from specific individual characteristics can be controlled by using the neutral condition as the baseline reaction of each individual.

The resulting response curves for the normalized pleasant condition can be found in figure 3.9.a, where the HR change curve of the control group appears in blue, and the HR change curve of the MDD group is illustrated in red. Figure 3.9.b, depicts the mean and the standard error derived from each group response represented again in blue and red for the control and the MDD group respectively across the three time windows. Similar, figures 3.9.c and 3.9.d illustrate the HR change curve for the corrected unpleasant and the mean and standard error bar plot respectively.

Regarding the statistical analysis, the table 3.7 reflects the ANOVA statistical values, where no interaction effect was found between the experimental factors MDD and FH for any experimental condition (pleasant - neutral and unpleasant - neutral) in any time window.

Collected in table 3.8, the statistical analyses of the main effect MDD revealed significant differences between groups for the unpleasant condition within the second ($t(81) = 1.745$, $p = .039$) and the third ($t(81) = 1.65$, $p = .046$) time windows but not within the first one, while no significant differences were found regarding the pleasant condition. On the other hand, no significant differences (neither for pleasant nor unpleasant conditions) emerged regarding the FH factor in any time window (table3. 8).

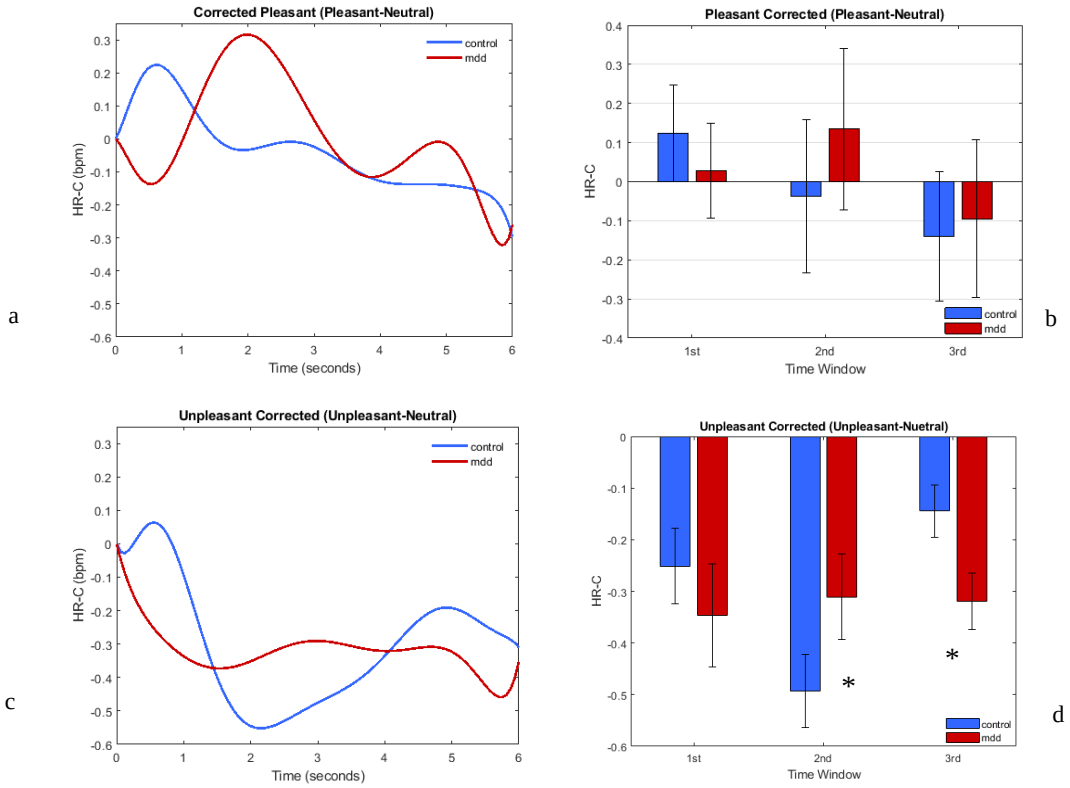


Figure 3.9 illustrates the response of each experimental group in blue and red for the control and the MDD group, respectively, for the pleasant (up) and unpleasant (down) conditions. Figures 3.9. a and 3.9. c located at the left side represent the heart rate curve response to pleasant and unpleasant conditions, respectively, measured in beats per minute across the six seconds or presentation time for each stimulus presentation. Figures 3.9. b and 3.9.d depict the mean and the standard error resulting from the averaged response of each experimental group (illustrated in red and blue for the control and the MDD group, respectively) for each time window. *emphasize the significant differences where the p-value is below .05.

Table 3.7.

Hear Rate Change: Interaction

	1st time window		2nd time window		3rd time window	
	pleasant - neutral	unpleasant - neutral	pleasant - neutral	unpleasant - neutral	pleasant - neutral	unpleasant - neutral
Interaction	.150 (.697)	.290 (.594)	1.590 (.211)	.190 (.671)	2.800 (.098)	.030 (.586)

Note. *p* values noted in brackets. * < .05. DF = 70.

Table 3.8.

Hear Rate Change: Post Hoc.

	1st time window		2nd time window		3rd time window	
	pleasant - neutral	unpleasant - neutral	pleasant - neutral	unpleasant - neutral	pleasant - neutral	unpleasant - neutral
Control vs. MDD	.542 (.589)	.776 (.239)	.593 (.554)	1.745 (.039)*	.176 (.860)	1.65 (.046) *
Negative vs. Positive	.120 (.904)	.637 (.526)	.575 (.567)	.541 (.590)	.753 (.316)	.039 (.968)

Note. *p* values noted in brackets. * < .05. DF-MDD = 81 | DF-FH = 50.

Table 3.7 depicts the interaction effect between both factors, MDD and FH, while Table 3.8 collects the resulting stats from the two-samples t-test analysis where the response across conditions (pleasant and unpleasant) is compared between experimental groups regarding MDD and he family history of MDD. T values are followed by the p values in brackets. * emphasize to the significant resulting p values below .05.

4 Discussion

4.1 Control group response

As described in previous works (see review Bradley, 2010), we find significant differences in the heart rate change under different experimental conditions (pleasant, neutral, and unpleasant) in healthy individuals. However, despite the clear differences regarding the response curves, we only find significant differences for the unpleasant condition when compared to both pleasant ($t(47) = 2.655$, $p = .010$) and neutral ($t(47) = 2.397$, $p = .020$) picture contents within the second time window (section 1 of results). According to the triphasic model of the cardiac response (Bradley, 2009), this time window corresponds to the maximal cardiac deceleration and would be related to the orienting response.

The lack of significant differences between the neutral and the pleasant categories suggests a downregulation of the cardiac response regarding the positive valence, despite the high arousing character of the erotic stimuli. However, no significant differences were found between erotic and familiar pictures (section 1.2 of results). Nonetheless, this attenuated response to erotic stimuli could be explained by the over-exposition of individuals to the erotic content, resulting in less striking stimuli and therefore, a lowered arousal. Under this framework, the existent differences under unpleasant stimulation (which has been also over exposed in the western culture) would be explained by the high relevance of this kind of stimuli for the survivor (Lang, Bradley and Curthbert, 1997). For unpleasant pictures, mutilation scenes provoked much greater HR deceleration than attack scenes ($t(47) = 2.275$, $p = .027$), suggesting the mutilation images as more relevant-arousing stimuli than the attack ones. Therefore, it is not surprising the lack of significant differences across time windows within the corrected pleasant curve (pleasant - neutral), while significant differences between the second and the first ($t(47) = 2.546$; $p = .014$) and the second and the third ($t(47) = 1.830$; $p = .053$) time window emerge for the corrected unpleasant condition (section 1.3 of results).

Moreover, the remarkable differences between the enhanced standard error within the normalized pleasant condition compared to the lowered standard error values exhibited for the normalized unpleasant response suggest a more robust and less heterogeneous normalized unpleasant response. In contrast, the normalized pleasant response exhibited by the same individuals suggests a more dispersed and heterogeneous pattern response under pleasant stimulation conditions. In the same line, the enhanced standard error exhibited within the first time window suggest a heterogeneous response pattern, where some individuals decelerate quickly while others show an initial short acceleration. Unlike Bradleys' (2009) model, our findings suggest that the sympathetic and parasympathetic innervations activity balance within the first time period varies across subjects.

4.2 MDD group response

Similar to the control group response, we find different performance in the cardiac response curves for each experimental condition where the only significant difference among MDD individuals occurs within the second time window between unpleasant and pleasant conditions ($t = 2.107$, $p = .042$, $df = 34$). No significant difference compared to the neutral condition emerges: despite the lack of significance, the faint accelerative component performed by the MDD group under pleasant conditions can be appreciated. However, the statistical analysis of the normalized response curves showed no significant differences across the different time windows for the pleasant condition (section 2.3, results)

Opposed to the control group, the statistical analysis revealed no significant differences regarding the subcategories of each experimental condition (section 2.2, results), neither across the different time windows within the normalized pleasant and unpleasant response curves, suggesting a flattered cardiac response to emotional stimuli. It is worth mentioning that unlike the control group, MDD individuals exhibited greater dispersion across the response patterns for both pleasant and unpleasant conditions.

4.3 Control group vs. MDD group

As previously described, to analyze the eventual differences across experimental conditions between experimental groups, we use the values from the normalized response curves as comparable measurements.

The normalized pleasant response curve shows an opposed response pattern for the control group (blue) compared to the MDD (red). While the first shows an initial acceleration followed by a flattered response, the second exhibits an initial deceleration followed by an accelerative component in the second time window. However, despite the differences between the curve-shapes for the normalized pleasant condition, no significant differences emerged for any of the three-time windows in the comparison between groups (section 3, results). This lack of significance originated from the dispersive response of the individuals (represented by the standard deviation) and the lack of significant differences between pleasant and neutral conditions for both groups.

Regarding the normalized unpleasant response curve, we find significant differences for the second ($t(81) = 1.745$, $p = .039$) and the third time windows ($t(81) = 1.65$, $p = .046$) but not for the first. While healthy individuals exhibit a large deceleration during the second time window followed by a cardiac acceleration, the MDD group displays a flat response curve. Moreover, the MDD group did not show significant differences across the three-time windows.

These results suggest, on the one hand, and consistently with our hypothesis and previous evidence on heart rate variability (Salomon et al., 2009; Duscheck et al., 2021), a blunted cardiac response where no differences appear during the six-time seconds of stimulus presentation. On the other hand, these results suggest an impaired cardiac reactivity during the orienting response.

Finally, unlike hypothesized, no significant differences were found regarding the factor of a familial load of depression. The ANOVA statistics does not show any significant

interaction. Similarly, the two-sample t-test did not show significant differences regarding the isolated FH factor.

Taken together, our results suggest that there is an impaired response pattern at the sympathetic and parasympathetic levels, behind the heart rate change response. Moreover, the lack of significant differences suggests that the impaired peripheral response occurs during current depression status but cannot be explained by familial backgrounds predisposing to suffer from depression, at least within the current sample.

1 Introduction

1.1 Background

The triphasic model of the cardiac response in terms of heart rate change measured in beats per minute (bpm) under relevant conditions, such as threat-related events or unpleasant stimulation, has been widely described when compared to not relevant neutral ones psychophysiology (see section 1, chapter 3). Concretely, the deceleration occurring during the second time window (within the 2nd and the 4th second after the stimulus presentation) has been related to the orienting response (Bradley et al., 2010) or orienting reflex (Skolov, 1060).

The orienting response has been linked to changes in the late positive potential or LPP (see section 1, chapter 2), where similarly to the cardiac response, the electrocortical wave response was greater for the high-arousing pleasant and unpleasant stimuli (Palomba et al., 1997; Schupp et al., 2000, Bradley et al., 2005; Moratti et al., 2004), when compared to less-arousing neutral stimuli, finding differences across the three different conditions.

The topographical distribution of this ERP component has been systematically related to occipital and parietal regions (Junghöfer et al., 2006; Keil et al., 2002) and fronto-parietal networks (Pardo et al., 1991; Moratti et al., 2004), demonstrating to be maximal at parietal regions (Bradley, 2010; Kayser, 2017) and always playing a preponderant role in the right hemisphere.

Whereas the enhanced response in early ERPs such as the N1 component to high-arousing stimuli has been read as a facilitation process to relevant features, the topographical distribution of the late positive wave, consistently with the attentional character of the orienting response, has been controversial: while Peter Lang propose an automatic allocation of resources to visual relevant stimuli, under the selective attention framework the changes in the LPP have been attributed to the cortical signature of attentional resources allocation to arousing stimuli over time (Moratti et al., 2004).

The study of the processing of emotional relevant stimuli across time in the motivated attention points not only to a specific brain region, but a more complex functional network involving frontal and parietal areas. In the study of these networks, the steady-state and the rapid visual stream have emerged as useful paradigms (further information about steady-state can be found in section 1, chapter 2). Due to the robust signal-to-noise ratio, steady state has demonstrated to be a robust tool in studying the electro-cortical activity across time (Müller and Hillyard, 2000) and consequently, for the study of the attention networks. Expressly, studies of visual-spatial selective attention have provided increased amplitudes for the attended stimuli leading frequency when compared to the non-attended one (Müller et al., 1998) and facilitate the study of featured-based attention (Müller and Hubner, 2002).

Critically, the role of the parietal cortex in emotional processing in patients with brain damage (see section 1 chapter 2) and measurements such as the LPP seems to partially overlap with the regions involved in the attentional processing and the associated fronto-parietal network (Moratti et al., 2004). Therefore, several studies have considered the role of emotion and arousal as features driving motivation attention under steady-state paradigms. Kemp et al. (2002) tested the role of the emotional valence at frontal regions using arousal-controlled stimuli under a 13 Hz steady-state paradigm, showing a decreased frontal induced response at frontal regions (Kemp et al., 2002). On the other hand, Keil et al. (2003) explored the impact of the high-arousal pleasant and unpleasant stimuli processing compared to low-arousal neutral under a steady-state paradigm where complex emotional scenes taken from IAPS flickered at a frequency of 10 Hz. Results have shown an increased stimulus-driven response frequency of 10 Hz greater at occipital and parietal regions (Keil et al., 2003). The regions evolved were later explored by Moratti et al. (2004) by using the same paradigm but measuring neuro-magnetic activity recorded by MEG. Due to the higher spatial resolution of this technique and the Minimum Norm Estimation (MNE), they could define the role of the fronto-parietal network with higher accuracy.

Later studies of Müller et al. (2013 and 2018) have deeper analyzed the role of the emotional and perceptual features in attentional processing using both steady-state and rapid visual stream presentation and IAPS complex emotional scenes to understand further the

role of emotions as a feature in the framework of the feature-based attention (Gundlach et al., 2013; Beckthtereva et al., 2018)

To date, the role of these brain areas seems quite robust. Moreover, the subcortical structures linking the ventral visual system, such as the pulvinar, have also been characterized as part of the attention network (Fernandez-Duque and Posner, 2001). On the other hand, the peripheral reactivity to different arousal categories has been widely replicated and, moreover, proposed as a signature of the oriented response and the late potential wave (Bradley, 2010). However, the relationship between the cortical and the peripheral reactivity, such as heart rate change, to different arousal and valence categories is still unclear.

1.2 Hypotheses

The current study explores the eventual relationship between the steady-state response and the heart rate change using the cardiac values obtained during the heart rate change analysis (see results chapter 3) within the second and the third presentation time windows as regressors for the steady-state activity presented in chapter 2.

Here we hypothesize a strong correlation across time between the superior parietal cortex and the second time-window of the heart rate change. Moreover, we hypothesize that this response is maximal within the second time window compared to the third under highly-arousal conditions compared to the pleasant. Aside, given the previously reported results (chapter 2 and Chapter 3), we also hypothesize that this correlation is more robust for healthy subjects than for the MDD patients.

However, it must be pointed out that despite of the lack of significant differences at the cardiac level regarding to the familiar load of depression, due to the significant differences obtained within the control group regarding the family history of depression in the ANCOVA analysis, we proceed to analyze also the eventual differences at this level.

2 Methods

Information about participants, diagnose and excluding criteria, stimuli and procedure can be found in the section *general methods*.

2.1.1 Participants

It must be pointed out that the total sample for the current study was composed of seventy-seven subjects (56 females, 72 right-handed. Mean age = 30.71; range 18 to 62 years) taken from the same sample used in chapter 3 (see methods section, chapter 3). Six participants out of the whole sample were excluded due to the impossibility of cardiac signal reconstruction. As mentioned in chapter 3, those individuals with unknown familiar history of depression were also excluded from the resulting sample.

More methodological concerns regarding data acquisition, signal preprocessing, and cortical source analysis of ssVEF can be found in the methods section of chapter 2. Preprocessing of the heart rate change data, and statistical analysis of heart rate change can be found in the results section, chapter 2.

2.1.2 Statistical analysis

The relationship of steady-state response with the heart rate response over time was estimated by SPM linear regression models, where the resulting mean value from the estimated heart rate change activity in terms of beats per minute within the second and the third time window (corresponding to the 2-4" and the 4-6" presentation time respectively) for each participant and condition was included as the main regressor. As previously mentioned in the methods section of chapter 3, the heart rate curves were normalized by subtracting the neutral condition to the experimental (Pleasant = pleasant – neutral; Unpleasant = Unpleasant - neutral). The resulting mean corrected MNI volumes, normalized by subtracting the neutral from each experimental condition (Pleasant = pleasant – neutral; Unpleasant = unpleasant - neutral), were used for the regression analysis. As previously

reported in chapter 2, the age of participants was included as a covariate in order to control eventual side-effects.

The regression coefficients were tested from the adjusted individual data estimated from the SPM ANCOVA, where correlation was considered as significant under .05 p value. To get rid of spurious correlations, eventual outliers were estimated from resulting vector-values for each condition with respect to the mean and the median, considering as an outlier those subjects for whose amplitude values were over two standard deviations from the mean or the median.

The eventual differences across groups regarding the experimental factors (MDD and FH) were tested by comparing the resulting values from the SPM regression; the interaction effect between factors was tested by a two-ways ANOVA, while on a second level analyses, the main effect of each isolated factor was tested by a two-samples t-test. Note that the sample size can differ across analyses due to the presence of outliers, which never exceeded the number of five and were estimated by the mean and the median values of each group distribution.

3 Results

3.1 Global sample analysis

3.1.1 HR change and unpleasant steady-state modulation

The results from the SPM regression analysis of the steady-state and the HR change during the second time window (from 2 to 4 seconds) in corrected unpleasant condition, are illustrated in figure 4.1.a, where two significant clusters emerges at the right parietal cortex ($t(69) = 4.78$; $k = 6313$; $p < .001$) and the inferior occipital gyrus ($t(69) = 4.66$; $k = 2101$; $p < .001$). Figures 4.1.b. and 4.1.c depicts the correlation at the right parietal cortex ($r = -.409$, $p < .001$) and the right inferior occipital gyrus ($r = -.339$. $p < .001$) during the second time-window. Correlations tests exhibit a strong negative tendency between ssVEF amplitude and HR change, where the more decreased cardiac response reflects higher steady-state amplitudes.

The resulting cluster from the SPM regression of the steady-state amplitude and the HR change during the third time window (from 4 to 6 seconds) in corrected unpleasant condition is represented in figure 4.2.a, where a significant cluster including left occipital and left fusiform gyrus ($t(69) = 4.30$; $k = 2722$; $p < .001$) emerges. Attached, Figure 4.2.b shows the negative correlation at left occipital / left fusiform gyrus and the ssVEF amplitude ($r = -.454$. $p < .001$) during the third time window.

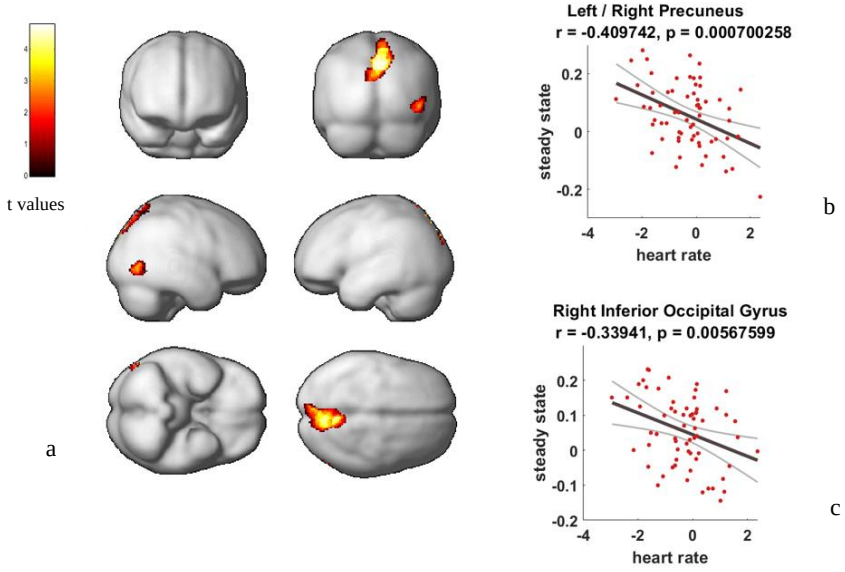
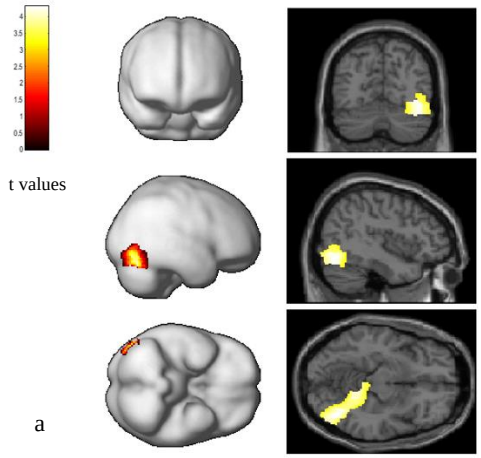


Figure 4.1.a depicts the topographical distribution of the significant values (t (69) = 3.212; p<.001) resulting from the unpleasant-neutral steady-state condition volumes regressed by the estimated mean values from the second time of window presentation (2-4“). Figures 4.1.b and 4.1.c on the right illustrate on garnet dots the spatial distribution of the correlation data. The black line and the gray curves represent the inverse tendency of the regression and the confidence interval (95%), respectively.



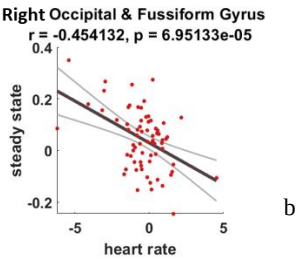


Figure 4.2.a shows the topographical distribution of the significant values (t (69) = 3.21; p<.001) resulting from the unpleasant-neutral steady-state condition volumes regressed by the estimated mean values from the third time window of presentation (4-6“). Figures 4.2. b on the right illustrates on garnet dots the spatial distribution of the correlation data. The black line and the gray curves represent the inverse tendency of the regression and the confidence interval (95%), respectively.

3.2 HR and pleasant steady-state modulation

The significant clusters resulting from the SPM regression of the ssVEF amplitude and the HR change values from the second time window in the corrected pleasant condition are illustrated in figure 4.3.a. One significant cluster arises at the central, left ($t(69) = 4.71$; $k = 4115$; $p < .001$) and another at right-central superior parietal cortex ($t(69) = 4.03$; $k = 105$, $p < .001$). Again, figures 4.3.b. and 4.3.c. presents the negative correlation between the HR change and the steady-state modulation at left ($r = -.548$, $p < .001$) and the right-central superior parietal cortex ($r = -.548$, $p < .001$) respectively where the greater heart rate change decrease is associated to higher ssVEF amplitude.

Figure 4.4.a. exhibits the resulting cluster from the regression of the ssVEF amplitude and the heart rate change during the third time-window of the corrected pleasant condition. One significant cluster located at the left superior parietal cortex ($t(69) = 3.69$; $k = 127$; $p < .001$) emerges. Aside, figure 4.4.b. illustrates the negative correlation of the regression in this cluster ($r = -.394$, $p < .001$), where again, greater cardiac deceleration implies greater ssVEF amplitude.

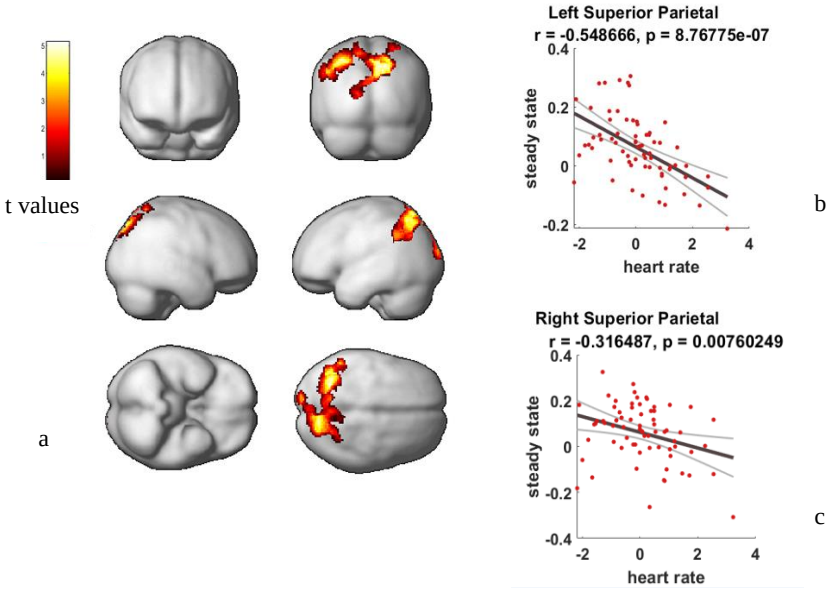
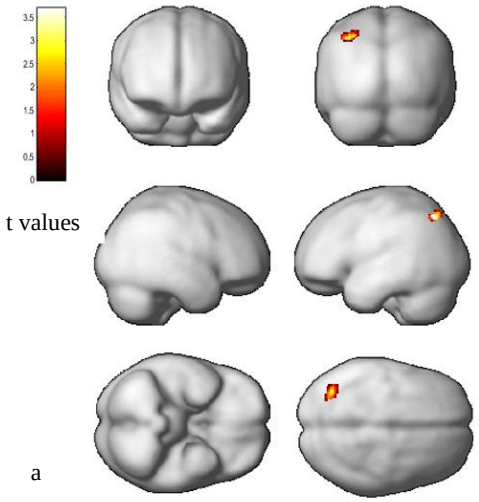
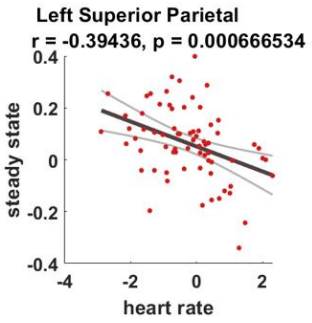


Figure 4.3.a shows the topographical distribution of the significant values (t (69) = 3.21; p<.001) resulting from the pleasant-neutral steady-state condition volumes regressed by the estimated mean values from the second time window of presentation (2-4“). Figures 4.3.b and 4.3.d on the right illustrate the spatial distribution of the correlation data on garnet dots. The black line and the gray curves represent the inverse tendency of the regression and the confidence interval (95%), respectively.



a



b

Figure 4.4.a shows the topographical distribution of the significant values (t (69) = 3.21; p<.001) resulting from the pleasant-neutral steady-state condition volumes regressed by the estimated mean values from the third time window of presentation (4-6“). Figures 4.4.b on the right illustrates on garnet dots the spatial distribution of the correlation data. The black line and the gray curves represent the inverse tendency of the regression and the confidence interval (95%), respectively.

3.3 Comparison between the relation between HR change and pleasure and unpleasure ssVEF modulation

To explore the differences in the topography of the resulting SPM regression analysis, the significant clusters for each condition were plotted within the same MNI brain map in different colors. Therefore, figure 4.5.a. illustrates the superposition of both the resulting SPM regression clusters for pleasant (cyan) and unpleasant (red) pictures across second (up) and the third (down) time windows. The figure 4.5.a shows a partial overlap at the parietal cortex for the second time window SPM regression (figure 4.5.a, up), while no overlapping clusters emerges for the third time window SPM regression (figure 4.5.a, down), where the topography shows two significant clusters among the left parietal cortex and the right occipital and fusiform gyrus.

In order to compare the differences in the topography of the resulting clusters from the SPM regression analysis for each time window (second and third time window) within the same condition, figure 4.5.b up illustrates the significant clusters of the SPM regression analyses for the unpleasant pictures presentation for the second (red) and the third (purple) time window (figure 4.5.b, up) plotted in the same MNI space. The resulting figure shows a change from parietal (red) to ventral occipital (purple) from the second to the third time window.

Below, figure 4.5.b. down illustrates the significant clusters of the SPM regression analyses for the pleasant picture presentation for the second (marine) and the third (cyan) time windows plotted in the same MNI space (figure 4.5.b, down). The resulting figure shows the overlapping clusters at the left superior parietal cortex for the second and the third time windows, being greater in size the resulting cluster for the second time window regression (marine) than for the third (cyan).

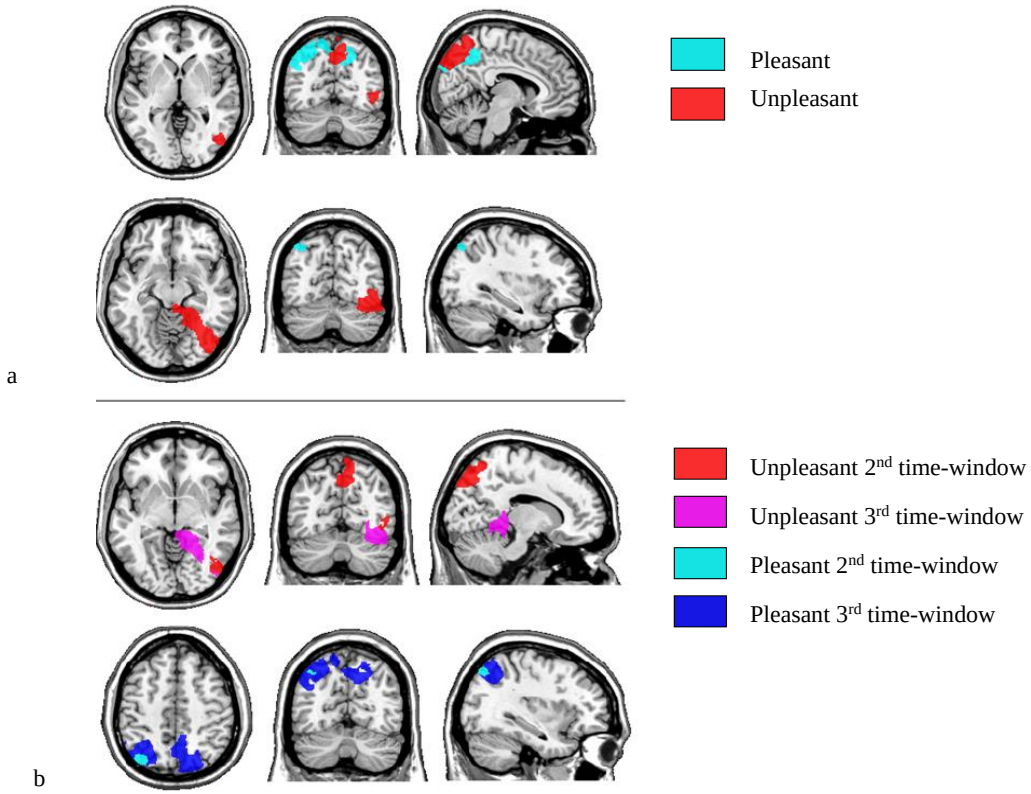


Figure 4.5.a illustrates regression significant clusters of both pleasant (cyan) and unpleasant (red) in the same MNI space for the second (up) and the third (down) time windows. Figure 4.5.b shows the resulting significant clusters from the unpleasant regression (up) for the second (red) and the third (purple) time window in the same MNI space, and from the pleasant regression (down) for the second (marine) and the third (cyan) time window.

3.4 Differences across experimental groups

Regarding the main hypotheses of the present chapter, we tested the eventual differences between the SPM regression analyses for both experimental factors, MDD and FH. Therefore, we performed independent t-test and two-ways ANOVA to analyze the main effects and the interaction effect across factors using the resulting values from the SPM regressions analysis from each emergent cluster for both, Pleasant and Unpleasant conditions (table 4.1 and 4.2). As illustrated in the table 4.1 and 4.2, no significant differences were found in the interaction between factors for pleasant nor unpleasant conditions (table 4.1 and 4.2). Similarly, no significant differences were found regarding main effects MDD and FH (table 4.1 and 4.2).

Table 4.1.

Heart Rate Change / steady-state regression: Unpleasant - Neutral

	Control vs. MDD			FH- vs. FH+			Interaction		
	t-value	p-value	DF	t-value	p-value	DF	F-value	p-value	DF
Second time-window									
- Superior parietal:	.2	.657	64	1.74	.191	64	2.62	.059	64
- Right occipital:	0	.987	70	.56	.456	70	.79	.502	70
Third time-window									
- Right occipital:	2.99	.088	70	.01	.922	70	1.12	.436	70

Note. *$p < .05$ | **$p < .01$.

Table 4.2.

Heart Rate Change / steady-state regression: Pleasant - Neutral

	Control vs. MDD			FH- vs. FH+			Interaction		
	t-value	p-value	DF	t-value	p-value	DF	F-value	p-value	DF
Second time-window									
- Left parietal:	.19	.661	69	1.82	.182	69	.8	.501	69
- Right parietal:	1.33	.253	69	1.87	.175	69	1.13	.344	69
Third time-window									
- Left parietal:	.34	.560	70	.08	.777	70	.42	.737	70

Note. *$p < .05$ | **$p < .01$.

Table 4.1. illustrates the statistical analyses of the eventual differences in the resulting SPM regressions for each significant cluster from the unpleasant picture presentation, regarding the main factors MDD and FH: form left to right, the two-sample t-test for the MDD factor, the two-sample t-test for FH factor, and the two-ways ANOVA for the interaction between both factors.

Table 4.2. illustrates the statistical analyses of the eventual differences in the resulting SPM regressions for each significant cluster from the pleasant picture presentation, regarding the main factors MDD and FH: form left to right, the two-sample t-test for the MDD factor, the two-sample t-test for FH factor, and the two-ways ANOVA for the interaction between both factors

4 Discussion

4.1 Depression

As described in section 2 of results, unlike our hypotheses, no significant differences were found when comparing the correlation between heart rate change deceleration and steady-state activity regarding the current depressed status, the familiar load of depression and the interaction between both factors. Despite the unexpected results, our data evidence that even in the presence of significant differences at both peripheral and central levels under current depression status, the correlation among both responses does not show significant differences.

This lack of significant differences could suggest on the one hand, that both systems (central and autonomic) could be proportionally affected, at least under MDD status, due that we find significant differences at both levels but not in the comparison between them. This way, the correlation between HR deceleration and the ssVEF amplitude would be stable independently from the MDD status (and of course, from the FH status). On the other hand, our results could be pointing to a non-differentiated integrative process for the autonomic related to central response. However, it is important to remind that the lack of significant differences does not imply the lack of differences, and therefore, this dissertation has a pure conjectural character.

Finally, despite the differences across conditions (pleasant- unpleasant | 2^{nd}-3^{rd} time window) described in following sections, congruent with previous evidences in attentional processing (Bradley, 2009; P. J. Lang & Bradley, 2010), the parietal cluster emerging in the SPM correlation analysis at the second time window reflects the critical role of the parietal cortex in the attentional processing of emotion relevant stimuli during the orienting response.

4.2 Valence

Regarding the valence dimension, we only find significant differences in the HR change between unpleasant and neutral stimuli. However, the significant correlation observed for the pleasant condition leads to interesting correlation patterns of steady-state response across time when compared to unpleasant ones, as illustrated in figure 5.a. these differences.

Moreover, even in the absence of significance at the HR change level, individuals exhibited different HR patterns across conditions (figure 4.1.b-c and 4.3.b-c): whereas unpleasant values shown a more negative tendency, and therefore, greater deceleration during the orienting response; pleasant values exhibited more positive values, especially for the second time window, representing a more attenuated pattern and consequently, a flattened orienting response when compared to unpleasant stimuli. This faint difference agrees with the idea of the biological relevance of the stimuli for survival, where more potentially dangerous items elicit maximal attentional responses and collecting, therefore, greater attentional resources in order to preserve life from potential threatening events.

Regarding the third time-window correlations, we also find a different pattern on the range values: while the cardiac response to unpleasant images represents a wider activation range (from -5 to 5), the response to pleasant complex scenes is narrower (from -3 to 2). This difference could be interpreted (again) as a more attenuated cardiac response within pleasurable stimulation, while the greater range of response within this time window for the unpleasant condition can be understood as different reactivity patterns more dependent on the individual response strategies. A recent study of de Echegaray and Moratti (2021) have related the different cardiac activation pattern under high arousing stimulation to different response strategies, where some individuals showed a cardiac deceleration related to attentional processing reflecting an orienting response, while others exhibited a cardiac acceleration related to motor activation, reflecting a fight/flight response (Echegaray & Moratti, 2021).

4.3 Orienting response

Our current results support the proposed attentional component of heart rate deceleration in orienting response (Bradley, 2009; Bradley et al., 2012; P. J. Lang & Bradley, 2010): On the one hand, the late positive wave measured with EEG has been related to the heart rate deceleration occurring between 2 and 4 seconds, and on the other, the LPP activation has shown to be maximal at parietal regions related to attentional processing. Current steady-state results accord with this evidence, showing a maximal correlation between HR bradycardia and ssVEF amplitude for high arousing emotional events in the right superior parietal cortex during this time window, highlighting the attentional component of the orienting response represented by cardiac deceleration in presence of emotional relevant visual stimuli.

As mentioned before, contrary to the hypothesis of current chapter, where weaker correlation values where hypothesized based on previously reported differences at both, central and autonomic levels regarding MDD, our results do not point to significant differences during the second time window. This evidence suggests that, despite the lower reactivity values during the orienting response of MDD patients, both levels consistent work during the orienting response.

1 Introduction

1.1 The role of the amygdale in the emotional processing

The role of the amygdala in emotional processing and specifically its role in fear responses have been widely described in psychophysiology (LeDoux, 2003). The amygdala is an almond-shaped nucleus located in the medial temporal lobe, situated at the anterior boundary of the hippocampus. Divided into several nuclei, the amygdala receives input connections from the thalamus and the hypothalamus where it also projects efferent fibers. This particular connectivity has led to the view that the amygdala is responsible for the integration of perceptual input from sense and viscera and provides a fast analysis from the environment, especially with information related to potential threat.

In this line, the study of patients with brain damage of the amygdala has provided supporting evidence of the role of the amygdale in the relevant emotional stimuli recognition. Anderson and Phelps (2001) described the impairment of individuals with bilateral amygdala lesions in perceiving the emotionally salient events, who did not exhibit an enhanced response to aversive stimuli compared to neutral content (Anderson and Phelps, 2001). Aside, patients with amygdala lesions have also shown impaired performance in conditioning tasks, where they did not exhibit conditioned autonomic responses to visual or auditory stimuli (Bechara et al., 1995). Consistently with this evidence, the stimulation of the amygdala in animals has resulted in higher levels of corticosterone and autonomic signs of fear and anxiety behaviors (Davis et al., 1992).

Further, consistent with human amygdala lesions studies, brain imaging studies such as fMRI have revealed the implication of the amygdala during fear conditioning in humans (Buchel et al., 1998; LaBar et al., 1998). fMRI studies have also revealed increased activation in the amygdala in emotional recall (Canli et al., 2000). Regarding the amygdala response under emotional exposure, Cahill et al. (1996) demonstrated an increased concentration of glucose in the amygdala by PET imaging, as individuals viewing highly arousal emotional film clips. Moreover, the number of videos recalled by the participants

when they were asked to remember the visualized videos several weeks later positively correlated to the glucose levels of the right amygdala during the film viewing (Cahill et al., 1996). A meta-analysis published by Costafreda et al. (2007) from 385 functional neuroimaging studies concluded that the amygdala activation was more likely to be found under emotional stimulation for most negative and positive emotions than for neutral stimuli. However, they found higher activation probabilities for fear and disgust than happiness (Costafreda et al., 2007). The relevant relationship between the amygdala and fear, specifically regarding fear conditioning, has been widely described by LeDoux (2003).

Neuroimaging studies have shown that the amygdala exhibits greater activation as a response not only to both pleasant and unpleasant emotional stimulation but to unpredicted stimulation patterns: Herry et al. (2007) reported increased amygdala reactivity to an unexpected stimulus when presented among a regular sequence of stimuli (Herry et al., 2007).

To date, the evidence seems quite clear about the amygdala's role in emotional processing under visual stimulation paradigms. Critically, Méndez-Bertolo et al. (2016), in a further step analysis, reported by intracranial EEG measures, increased amygdala reactivity to specific social aversive items such as fearful faces in short time latencies (from 74 ms after stimulus onset), faster than the early fear components observed in the primary visual cortex, led by the magnocellular inputs of the amygdala (Méndez-Bertolo et al., 2016).

1.2 Implications of the amygdale in MDD

The preponderant role of the amygdala in emotional processing and the disturbing emotional processing in depression leads to the question about the amygdala's role within the depression framework.

On the one hand, the previous evidence in this field have provided inconsistent results regarding the relative volume of the amygdala in current depression status: whereas some authors have reported a decreased amygdala volume in current depression (Sheline et al.,

1998; Hastings et al., 2004), other researchers have found no significant differences in amygdala volume when compared MDD patients and healthy individuals (Axelson et al., 1993; Coffey et al., 1993). Interestingly, other studies have reported opposing evidence, where MDD patients exhibited larger amygdala volumes (Bremer et al., 2000). It is worth mentioning that regarding gender differences, unlike Sheline et al. (1998), Hastings et al. (2004) reported decreased amygdala volumes only for females but not for males MDD patients. Critically, Hamilton et al. (2008) revealed in a meta-analysis that the presence of medication could explain these controversial findings: they found that whereas unmedicated individuals demonstrated decreased amygdala volumes, those under pharmacological treatment exhibited increased volume. This surprising effect has been considered in the same study as consistent with the hypothesis of the increased presence of neurotrophic factors derived from the antidepressant treatment, which results in more neurogenesis (Perera et al., 2007) and protection to the glucocorticoid toxicity, which could explain of the decreased volume in non-medicated MDD individuals (Hamilton, Siemer and Gotlib, 2008).

Further, studies about the amygdala during both resting state and emotional exposure have brought a disruptive amygdale behavior. Drevets et al. (1992) found that the blood flow in the left amygdala was increased for individuals suffering from depression compared to healthy subjects. Additionally, they found a positive correlation between the left amygdala activation pattern and the Hamilton depression scale scoring (Drevets et al., 1992). Moreover, this blood flow pattern was also tested in individuals under remission, where no significant differences were found, suggesting that the left amygdala could represent a trait marker of depression (Drevets et al., 2002).

fMRI studies have also supplied evidence of increased amygdala activity under emotional exposure in individuals suffering from depression: Sheline et al. (2001) reported increased left amygdale activity during fearful faces exposure and reduced bilateral amygdala to neutral faces. Regarding the right amygdale, no significant differences were found when compared to controls (Sheline et al., 2001).

Similar results were reported by Siegle et al. (2002) using an emotional words presentation paradigm. They found that whereas healthy individuals' responses decayed within the 10 seconds after stimuli presentation, depressed individuals displayed a sustained response to negative words until the next stimulus presentation (Siegle et al. 2002). Similar to Drevets' study (2002), Siegle reported a positive correlation between amygdala activation and ruminative levels.

Consistent results were provided by Hamilton and Gotlib (2008), who reported increased amygdala activation to negative IAPS pictures in depressed individuals but not for neutral or pleasant pictures in comparison with healthy subjects. Moreover, they discovered that the increased activation of the right amygdala correlated with the later remembered negative stimuli (Hamilton and Gotlib 2008).

Unlike Drevets' (2002) findings, where the tonic hyperexcitability of the amygdala did not exhibit significantly higher activity under remission, Hooley et al. (2009) reported persistently increased response to negative stimuli within remission phases of depression. Therefore, the hyperreactivity of the amygdala to negative emotional stimuli has been claimed as a potential risk factor of depression (Hamilton, Furman, and Gotlib, 2016).

1.3 Hypotheses

Based on previously reported evidence of amygdale volume, we hypothesize differences in the volume of the amygdala regarding current depression status. Due to the pharmacological treatment of the MDD patients of our sample, we hypothesize greater amygdala volumes in depressed patients compared to healthy individuals.

Regarding the hyperexcitability of the amygdala during negative emotional exposure interpreted as a potential risk factor for depression despite the discrepancy with tonic activity, we will also explore the eventual differences in the volume of the amygdale regarding family load of depression.

Additionally, we will test the eventual correlation between the amygdala volume and the ssVEF amplitude during emotional picture viewing.

Finally, similar to Drevets and Siegle (2002), we will test the positive correlation between the amygdala volume and the depression symptomatology measured by the Hamilton Depression Rating Scale, here we hypothesize a positive correlation between the volume of the amygdala and the severity of the depression symptoms.

Note: due to the controversial capability to record the magnetic signal from deep sources, and due to the spherical shape of the amygdala and shortage amount of trials based on the signal-to-noise requirements of the current steady-state paradigm, we discard the chance of finding reliable amygdala activity using MEG. Therefore, in the current chapter, we perform statistical analysis concerning the amygdala volume itself and the relative amygdala volume as variables mediating the cortical response obtained by the steady-state visual evoked field recorded under our current experimental design.

2 Methods

Information about participants, diagnosis and exclusion criteria, stimuli, and procedure can be found in general methods. For a more detailed description of the steady-state response, see methods chapter 2.

2.1 Participants

The sample consisted of fourteen healthy subjects (nine righthanded females) and ten depressed individuals (seven righthanded females). Mean age 23.9 years old. The low sample of the present study is due to the impossibility of obtaining the MRI scans for the rest of the sample [6].

2.2 MRI Acquisition and Analysis

Magnetic resonance scans were acquired using a 3 Tesla MRI scanner (Signa HDxt General Electric, Waukesha, USA) located at the Fundación CIEN of the Reina Sofia Foundation for Alzheimer's Research, Madrid, Spain. The Whole-brain T1 images were acquired by 3D sequential fast spoiled gradient recalled, resulting in 166 sagittal slices of 1mm thickness, with an overall non-isotropic image resolution of 1x.5x.5 mm. The scan image segmentation and the voxel-based morphometry were performed by the Statistical Parametric Mapping toolbox implemented for Matlab software (SPM12) for axial, coronal, and sagittal slices at 50 mT/m.

The anatomical regions of interest (amygdala and total brain volume) were extracted from the resulting automatic image segmentation performed for each participant's T1 image by Freesurfer 5.3.0 software (https://surfer.nmr.mgh.harvard.edu/) and manually corrected

[6] The high drop of participants from the whole sample to those with MRI scans is due to the low adhesion participants, which commonly refused to continue until the end step of the study (the MRI) after the clinical evaluation and the MEG recording.

after visual inspection. The final volumes of the amygdala were estimated from the resulting voxel-based segmentation obtained from the corrected Freesurfer segmentation values converted to mm3. The relative volume of the amygdala was estimated in mm3 as a proportion of the total cerebral volume (e.g. Vakili et al., 2000; Bremner et al., 2002; Hastings et al., 2004) (amygdale volume / total cerebral volume) for both amygdalae bodies, separately and together.

2.3 Statistical analysis

Due to the different statistical approaches followed for each section analysis developed in the current chapter, specification for each specific statistical procedure can be found in its corresponding apart within the results section.

3 Results

3.1 Amygdala relative volume.

The eventual differences in the amygdale volume regarding current depression and the familiar load of depression were tested by a two ways ANOVA, where no significant interaction could be observed (table 5.1). Alike, no significant differences were found regarding the factor family history of depression.

On the other hand, we found significant differences in the two-samples t-test analysis regarding to the current status of depression, which showed significant differences in the left (t (22) = 2.337; p = .028), right (t (22) = 2.219; p = .037) and congruently, the bilateral relative amygdala volume (t (22) = 2.409; p = .024) (table 5.1, figure 5.1). The differences for each statistical analysis regarding the differences in the left, right and both anygdala bodies, are represented in the figure 5.1, where the bar plots represent the mean volume values for the healthy control group (blue) and for the MDD group (red). Standard errors are illustrated by the black bars within plots.

Table 5.1.

Amygdala Stats.

	Control vs. MDD			FH- vs. FH+			Interaction		
	t-value	p-value	DF	t-value	p-value	DF	F-value	p-value	DF
Left Amygdala	2.337	.028 *	22	.291	.773	22	.26	.617	23
Right Amygdala	2.219	.037 *	22	.193	.848	22	3.11	.092	23
Bilateral Amygdala	2.409	.024 *	22	.249	.805	22	1.23	.280	23

Note. *$p < .05$ | **$p < .01$.

Table 5.1 depicts the results from the statistical analysis of amygdala volume relative to the total cerebral volume (TCV) for the main effects of depression and the familial load of depression and the interaction of both factors, where only significant differences ($p < .05$) are found for the main effect of depression.

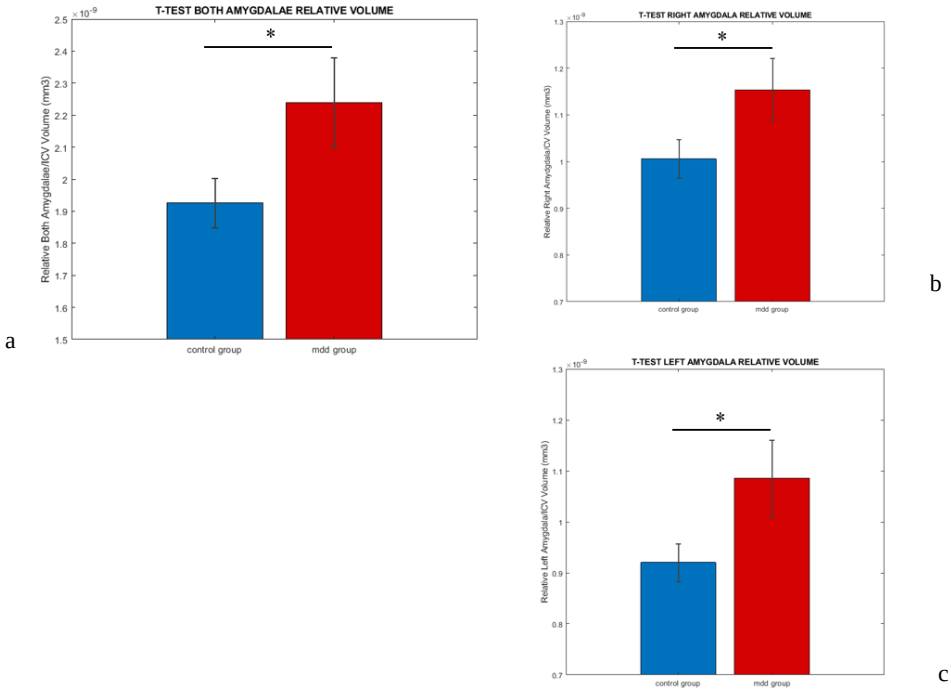


Figure 5.1.a. Bar plot illustrates the resulting mean values for the bilateral amygdale volume relative to the TBV indicated in the y axis in mm^3 and represented in blue for the control group and in garnet for the MDD group, specified in x axis. Standard errors are represented in black brackets. Figure 1.b. and c. show the same results for the left and the right amygdale, respectively. Note that * identify significant differences for $p < .05$ (complete values can be found in table 5.1).

3.2 Amygdala relative volume as a covariate comparing ssVEF amplitude of MDD patients and healthy controls

The aim of the current section is to analyze the eventual relationship between the amygdala volume relative to the total brain volume and the ssVEF amplitude modulation by emotion. Therefore, we included the amygdala relative volume as a covariate in the SPM analysis.

Regarding the amygdala volume we found significant differences only for the MDD factor and not for the interaction with the FH, neither for the FH isolated factor (see table 5.1, section 1 of results). We tested the effect of the relative volume of amygdala as a covariate in the SPM two-samples t-test for independent measures where the ssVEF amplitude from MDD patients and healthy controls is compared for the pleasant, unpleasant and arousal modulation.

3.3 Amygdala relative volume as a covariate of the ssVEF during pleasant pictures presentation

No significant clusters were found in the SPM two-samples t-test comparison of MDD patients and healthy controls for pleasant pictures within the current sample, with and without the amygdala relative volume covariate.[7]

3.4 Amygdala relative volume as a covariate of the ssVEF during arousal modulation

The results for the two-samples t-test analysis with the relative amygdala volume as covariate are illustrated in figure 5.2.a, where one significant cluster located at the right superior parietal cortex emerges ($t(18) = 3.72$; $p < .01$; $k = 574$ voxels). Aside, figure 5.2.b. and c. shows the results of the same t-test analysis introducing the amygdala relative volume

[7] To keep the same statistical standards, the reported p-value was restricted to (at least) below .01.

as a covariate for the t-test where p-value threshold is below .01 (t (18) = 3.99; k = 774; p < .01) and .001 (t (18) = 3.99; k = 69; p < .001) respectively.

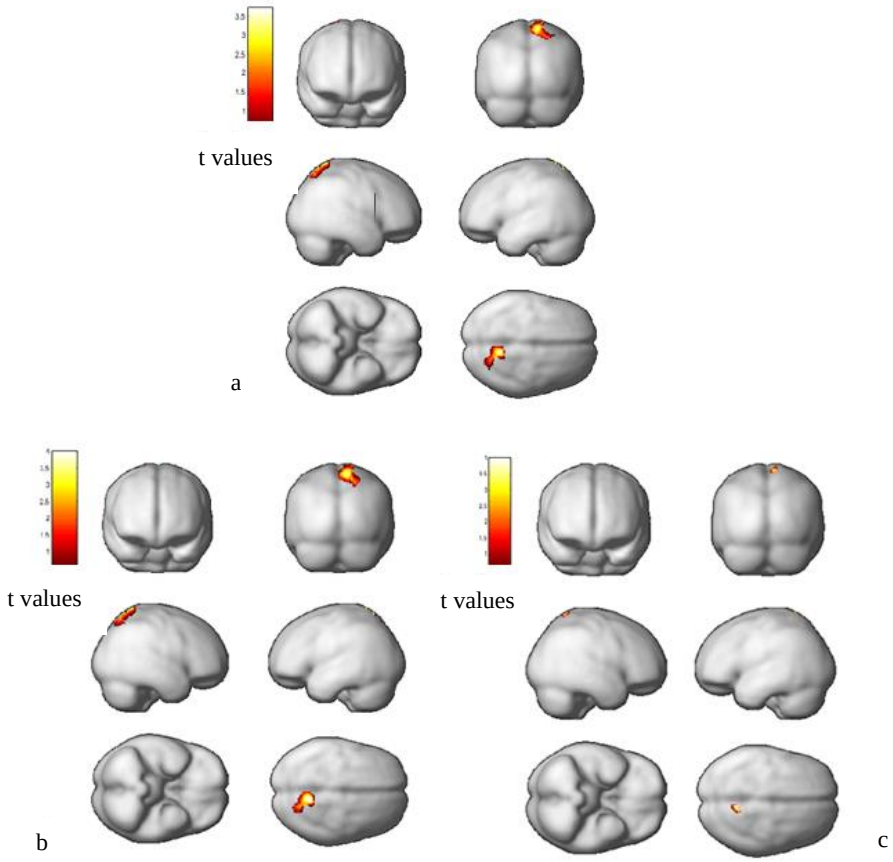


Figure 5.2.a collects the significant cluster distribution resulting from the SPM t-test analysis of the steady-state response during arousal modulation [(pleasant + unpleasant). /2] for the current sample. Figure 5.2.b and c illustrate the SPM t-test analysis introducing the relative amygdala volume as covariate thresholded at .01 and .001 *p* values respectively

3.5 Amygdala relative volume as a covariate of the ssVEF during unpleasant pictures

The current section depicts the SPM two-samples t-test where ssVEF amplitude of MDD patients and healthy controls are compared during unpleasant pictures presentation. Figures 5.3.1. and 5.3.b. illustrate the significant cluster resulting from the SPM t-test analysis corresponding to the unpleasant condition without ($t(18) = 2.87$; $p < .01$; $k = 209$) and with ($t(18) = 2.98$; $p < .01$; $k = 467$) the amygdala relative volume covariate respectively.

The t-test including relative amygdala volume for left and right amygdala volumes separately are not included in the current section due the overlapping regions between them and with the bilateral amygdala volume.

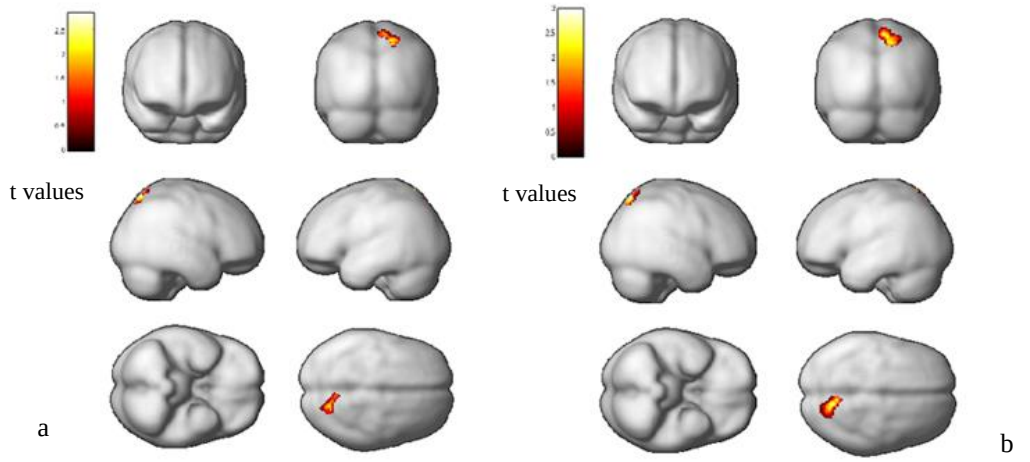


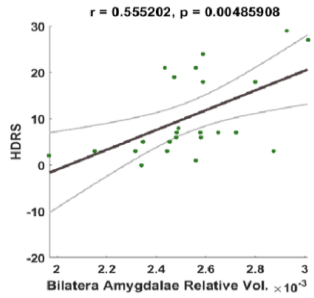
Figure 5.3 illustrates the significant cluster distribution from the SPM t-test analysis of the steady-state response under corrected unpleasant condition (unpleasant-neutral). Whereas figure 5.3.a. shows the resulting t-test, figure 5.3.b shows the t-test where amygdala relative volume is introduced as a covariate. Both analyses are thresholded at $p < .01$; $K > 100$ voxels.

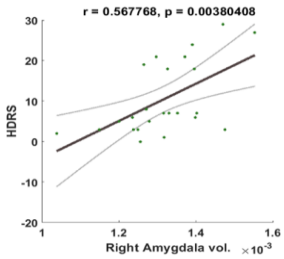
3.6 Amygdala relative volume in MDD symptom severity

As previously reported by Siegle and Drevet (2002), one of the aims of the current study was to explore the eventual relationship between the amygdala volume and the severity of the depression symptoms. Therefore, we use the relative amygdala volume as a predictor for the severity of the symptoms of major depression estimated by the Hamilton Depression Rating Scale (HDRS) (see general methods).

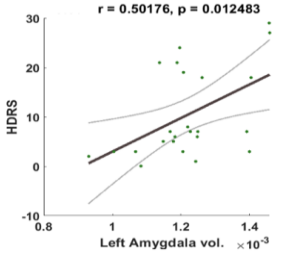
The correlation between the bilateral relative amygdala volume estimated in mm^3 and the HDRS scores is illustrated by figure 5.4.a, where results indicate a significant positive correlation between them (r = .555; p = .004), where the greater amygdala volume predicts higher HDRS ratings. Similar to bilateral amygdala bodies, significant positive correlations were found for the right (r = .567; p = .003) and the left (r = .501; p = .012) amygdala relative volume bodies, illustrated in the figures 5.4.b. and 5.4.c. respectively.

a





b



c

Figure 5.4.a-b-c illustrate the significant positive correlation between the relative amygdala volume for bilateral amygdalae bodies, right and left amygdala volumes, respectively, where the relative amygdala volume introduced as predictor indicated at the *x* axis in mm^3 and the HDRS is indicated in the *y* axis.

4 Discussion

4.1 Amygdala volume

Regarding the relative amygdala volume estimated to the total brain volume (section 1, results) similar to previously reported results, we find significant differences regarding the current status of depression, being this greater for the MDD individuals when compared to healthy control subjects (Axelson et al., 1993; Coffey et al., 1993; Hamilton, Siemer and Gotlib, 2008). Moreover, according to Hamilton et al. (2008) meta-analysis, the obtained results under our MDD sample, which incurs in pharmacological treatment, supports the proposed idea about the role of pharmacology in the increased amygdala volume through the neurotrophic factors and the glucocorticoid excitotoxicity protection under treatment. However, the lack of a control medication-free group restricts the supporting capability to this hypothesis.

Nevertheless, the fact that no significant differences appeared at the family history of depression level, and neither in the interaction effect (see table 5.1, section 1 of results) indicates that, under the lack of evidence of increased amygdala volume related to depression vulnerability (Hooley et al., 2009), the role of the pharmacological treatment in the volume growth exhibits an exciting target for future studies.

Regarding the statistical differences across groups, unlike some previously reported results, we find similar significant differences for the bilateral amygdalae and the right and left amygdala bodies separately (table 5.1, section 1, results).

Relative to the amygdala volume role as a signature of the potential risk factor for depression, the two-samples t-test where the amygdala relative volume of MDD patients is compared to the amygdala relative volume of healthy control subjects provided no significant differences. Moreover, analysis of the interaction of the FH with the current status of depression tested by the ANOVA (see table 5.1, section 1 of results), shown no significant interaction effect between factors. However, it is worth mentioning that previous work proposing the amygdala as a potential risk factor has based its hypothesis on the

hyperexcitability of the amygdala and not on the volume of this one, suggesting that both measures would not be coming together under premorbid stages of depression.

However, taking together previous evidence and the current study results, the concomitance of the increased volume in medicated MDD patients and the over-reactivity of the amygdala seem to be quite robust (Sheline et al., 2001; Siegle et al., 2002; Hamilton and Gotlib 2008).

4.2 Amygdala volume and the ssVEF amplitude

Based on this concomitance of the increased volume and the over-reactivity of the amygdala in medicated MDD patients, and the eventual influence of the amygdala on the cortical response to highly arousing stimulation (Anderson and Phelps, 2001; Méndez-Bertolo et al., 2016), we explore the eventual influence of the relative amygdala volume and the ssVEF amplitude introducing the amygdala relative volume as a covariate in the SPM t-test.

As can be appreciated in figure 2 of results, the topographical allocation cluster (right superior parietal cortex) does not significantly differ across conditions (arousal and unpleasant). However, the significant cluster size for the arousal SPM t-test varies as a function of the amygdala relative volume from 574 to 774 voxels when introduced as a covariate. Moreover, whereas no cluster survived for the t-test without the amygdala at $p < .001$ threshold, a smaller but strongly significant cluster (69 voxels) also located at the right superior parietal resist to the $p < .001$ analysis when the amygdala relative volume is introduced as a covariate (see figure 5.2, section 2 of results).

Regarding the corrected unpleasant (unpleasant - neutral), similar to the arousal, whereas the SPM significant cluster location does not change significantly among the superior parietal cortex (see figure 5.3, section 2 of results), different cluster sizes in favor of the steady-state amygdala covariate analysis are obtained (209 vs. 467 voxels). On the

other hand, t values slightly differ between the t-test with ($t(18) = 2.98$) and without ($t(18) = 2.87$) the amygdala covariate (section 2 of results). Unlike arousal modulation condition, no significant cluster survived to p-value thresholded below .001.

Importantly, the fact that the local topography did not change but increased at the superior parietal cortex suggest the direct relationship of the increased (and eventually, overreacting) amygdala in the attentional processing of salient arousing stimuli revealed by the steady-state response under current depression status (see chapter 2). However, is worth mentioning that, while no significant results were found in the SPM two-samples t-test for pleasant pictures (p threshold below .01), the significant differences for the unpleasant condition overlap with the arousal modulation topography.

Despite that the resulting cluster for the unpleasant pictures is smaller when compared to the arousal SPM covariate t-test, regions between unpleasant and arousal modulation conditions partially overlap, suggesting the preponderant role of the unpleasant high arousing stimuli in the right superior parietal cortex ssVEF amplitude.

However, the greater amplitude obtained in the SPM covariate t-test for arousal modulation between MDD patients and healthy subjects, suggest a stronger relationship between the amygdala and the ssVEF amplitude at the right superior parietal cortex in the arousal modulation, further than the negative arousing pictures.

Finally, unlike previously reported results which highlights the preponderant role of the right amygdala under highly arousing stimulation (Cahill et al., 1996), we did not find any significant difference in our correlations between left, right, and bilateral amygdala bodies.

4.3 Amygdala volume in MDD severity symptoms

Consistently with previous evidence in the correlation between amygdala activation and the HDRS scoring (Drevets et al., 1992) and the rumination (Siegle et al., 2002), here we demonstrate the significant positive correlation between the amygdala relative volume

and the severity of the MDD symptoms estimated by the HDRS scoring, where the greater relative volume predicts higher HDRS scores.

Unlike Drevets et al. (1992), who reported significant correlation only for the left amygdala volume, here we show the significant positive correlation for all; bilateral, left, and right amygdala bodies volumes (section 3, results). Moreover, our results suggest that the correlation results are much more significant for the right (p = 003) than for the left (p = 012) amygdala volume. However, unlike Drevets' studies based on amygdala activation, our results are based on the volume, which could explain the mismatching results.

Finally, the preponderant role of the right amygdala in the correlation with the MDD symptoms seems consistent with previous evidence of Hamilton and Gotlib (2008), where the increased right activation correlated with the higher probabilities of remembering previously presented emotional stimuli in posterior recalls (Hamilton and Gotlib, 2008).

Chapter 6. General Discussion

The aim of the present work was to understand and characterize the dysfunction of the attentional processing of emotional stimuli involved in the major depressive disorder and its relationship with the presence of family history of depression at central and autonomous nervous system. Therefore, we designed a passive viewing task where emotional (pleasant and unpleasant) and neutral images were presented on a steady-state paradigm to both, MDD patients and healthy individuals with and without family history of depression. Further, based on previous evidence on brain damaged patients (Shimoda & Robinson, 1999) and studies based on attentional paradigms (Kayser, 2000; Kayser et al., 2017; Moratti et al., 2004, 2008, 2015) we hypothesized the key role of the right temporo-parietal cortex in the characteristic attentional dysfunction of depression, relying on the family history of depression.

The analysis of the cortical activity revealed differences in the ssVEF amplitude during arousal modulation regarding both, current status of depression and the family history of depression: With respect to the current status of MDD, consistent with previous evidence (Kayser, 2000; Kayser et al., 2017; Moratti et al., 2008) we found a reduced ssVEF amplitude for the MDD group at the right superior parietal and the right frontal cortices. These results fit with the conceptualized idea of a blunted response of the attentional network in MDD and the proposed idea of Emotion Context Insensibility (Bylsma, 2021).

However, regarding the family history of depression, contrary to our hypotheses, we found an enhanced ssVEF amplitude in those healthy subjects with family history of depression in the right superior parietal cortex and the left superior frontal gyrus compared to healthy individuals without family history of depression. Further, we found an opposed tendency in the Right middle frontal gyrus, where healthy control subjects with family history of depression exhibited decreased ssVEF amplitudes compared to healthy control subjects without family history of depression.

Interestingly, contrary to our hypotheses, the post hoc analysis of the interaction in the SPM ANCOVA did not show these differences within the MDD group regarding the family history of depression. Here we speculate about a systemic failure of the fronto-parietal network in the current depressed status, which would be masking the impact of the family history of depression in this group. Importantly, after chi-square analysis of the sample distribution, we found significant differences regarding the MDD main effect at frontal and parietal regions. These results support the proposed Idea of the impaired right fronto-parietal attentional network under current status of depression. Moreover, we found no overlap between the regions involved in the ANCOVA interaction and the main effect of depression. However, contrary to previous evidence (Robinson & Shimoda, 1999) our results suggest the high relevance of both, frontal and parietal regions in family history of depression, and therefore, in the predisposition to suffer from MDD.

Critically, the analysis of the ssVEF amplitude of corrected unpleasant (unpleasant - neutral) pictures, showed the same direction than the arousal modulation in the same regions (figure 2.1.1.b of results, chapter 2). This finding suggests that, aligned to our hypotheses, the highly arousing unpleasant stimuli would be leading the differences in the arousal modulation. Further, regarding the main effect of depression, we find an overlapping cluster between the corrected unpleasant and the arousal modulation (figure 2.1.2.b of results, chapter 2), supporting the predominant role of the highly emotional pictures in the attentional processing during depression.

However, contrary to the main hypothesis of this thesis, the analysis did not reveal the temporo-parietal junction as a key region in the attentional processing of highly arousing emotional pictures regarding the family history of depression in healthy control subjects and MDD patients. It could be due to the lack of analysis of the family history of depression in healthy subjects in previous evidences (Moratti, 2015) and to the lower spatial resolution of previously employed techniques such as EEG of previous studies (Kaysser, 2017). Nonetheless, regarding the main hypothesis of this thesis about the impact of the family history of depression as endophenotype of depression, our results point to an unbalanced activation pattern of the fronto-parietal network in presence of family history of depression.

On the other hand, the analysis of the SPM ANCOVA of the corrected pleasant (pleasant - neutral) pictures, showed a blunted ssVEF amplitude for those participants with family history of depression independently from the current depression status in the right precentral gyrus (figure 2.3.1.a of results, chapter 2). Previous works have shown enhanced amplitudes in right temporo-occipital regions during pleasant images presentation (Junghöfer et al., 2001; Schupp et al., 2004; Shupp et al., 2007; Hinojosa et al., 2009): under this framework, our results suggest a blunted response of temporo-parietal regions to pleasant stimuli in the presence of family history of depression. Critically, results show significant difference as a function of the family history of depression for both, healthy controls an MDD patients.

Despite that this region fits with our main hypothesis, it does not fit with the highly arousal emotional stimuli results, and contrary to our hypotheses, does not seem to play a role in the current status of depression. However, this result suggests that the temporo-parietal cortex would be playing an important role in the family history of depression in the pleasant emotional stimuli processing.

Finally, the left middle frontal gyrus exhibits an opposed tendency under pleasant and unpleasant pictures within the healthy control group: while this region showed an enhanced amplitude in the FH+ group relative to the FH- in the modulation by unpleasant pictures, it showed an opposed tendency in the modulation by pleasant pictures, where the FH+ group exhibited a reduced ssVEF amplitude relative to the FH-. The relative enhanced activation in this region in healthy subjects has been related to higher positive mood, and therefore interpreted as an approach tendency to pleasant stimuli (Heller, 1997; Davidson, 2003; Harnon-Jones et al., 2010). Taken together, our results invite to consider the reduced amplitude of the FH+ group relative to FH- as an impaired approach tendency to pleasant pictures, while this approach tendency would be enhanced to unpleasant stimuli when compared to FH-.

Further than the characterization of the central neural attentional networking involved in the MDD and the family history of depression as an endophenotype, one critical goal of

the present work based on previous evidence of abnormal cardiac activity in patients suffering from MDD (see meta-analysis Kemp et al., 2010; Fraguas et al., 2007; Phillips 2010; Solomon et al., 2013; Barrione et al., 2018; J.Zhu et al., 2019) and the abnormal cardiac activity as a risk factor for depression (Rottenberg et al., 2005; Salomon et al., 2013), was to test the differences regarding the autonomic response in MDD and FH, characterized by a blunted response of the HR change as a reaction to highly arousing emotional pictures.

In this direction, the analysis of the HR change during emotional pictures presentation revealed significant differences regarding to the MDD: Consistent with previous reported results based on heart rate variability, our data provide supporting evidence of a blunted cardiac response in the MDD, where no significant differences were found across time windows for the corrected pleasant and unpleasant curves (figure 3.8 and table 3.6 from results, chapter 3). This lack of differences regarding the phasic response of HR change to emotional stimuli across time windows, suggests an attenuated orienting response to highly emotional stimuli (see Bradley, 2010).

However, the differences across time can be appreciated within the healthy control group for the second and the third time windows of the corrected unpleasant curve. Moreover, the statistical t-test comparison between MDD and control group shows significant differences in this time windows, highlighting the attenuated autonomous response to highly arousing stimuli, and hence, reflecting the sympathetic and parasympathetic alteration in the MDD. However, contrary to our hypotheses, no significant differences were found in the HR change regarding the FH factor: neither for the interaction nor for the main effect of FH (table 3.7 and 3.8 from results, chapter 3).

Previous studies in the orienting response have related the cardiac deceleration to the late positive wave in healthy subjects, which is maximal at parietal regions in EEG recordings (see Bradley, 2010). Due the evidence of the blunted HR change response of the MDD group as a signature of the impaired orienting response captured in the chapter 3, we explored its relationship with the cortical ssVEF amplitude.

The regression analysis of the ssVEF and the HR change showed the relationship between the right parietal cortex and the HR change deceleration, providing strong evidence of the attentional character of the orienting response for both, pleasant and unpleasant pictures. Moreover, while the HR deceleration seems to be related to the superior parietal cortex for both pleasant and unpleasant pictures, the regression analysis for the third time window revealed a strong correlation with the ventral stream and the right fusiform gyrus for the unpleasant pictures.

However, the lack of differences in this cortico-cardiac relationship in the orienting response regarding the MDD and the FH (table 4.1 and 4.2 from results, chapter 4) points to the same pattern response for all groups independently from the central and the autonomic differences in the attentional processing, which would be not affected in MDD and FH despite the isolated differences at the cardiac and cortical levels.

Finally, the role of the amygdala in the emotional processing has been widely described in the literature (see LeDoux 2003, Méndez-Bertolo et al., 2016) and in the MDD (see Hamilton, Siemer and Gotlib, 2008). Moreover, the differences in this structure have been related to the severity of the MDD symptoms (Drevets et al., 2002; Siegle et al., 2002). Therefore, the last objective of the present work was to analyze the eventual differences in the volumetry and its eventual relationship with the ssVEF amplitude during highly arousing images exposure. Consistent with some previous evidence (see meta-analysis Hamilton, 2008), the statistical analysis revealed the greater volume of the amygdala bodies of MDD patients compared to healthy control subjects. Critically, our results support the notion of the enhanced volume of the amygdala of MDD patients under the presence of pharmacological treatment. However, contrary to our hypothesis and to some prior evidences pointing to the hyperreactivity of the amygdala as a potential risk factor of depression (Hamilton, Furman, and Gotlib, 2016), no differences were found in the amygdala volume regarding the FH (table 5.1 from results, chapter 5).

Consistent with previous evidence of the severity of the MDD symptoms and the amygdala volume (Drevets et al., 2002; Siegle et al., 2002), the regression analysis of the

amygdala volume and the Hamilton Depression Rating Scale revealed a consistent positive correlation between the amygdala volume and the HDRS scores. Further, the t-test analysis between MDD patients and healthy controls revealed that the cluster size of significant clusters resulting from the SPM t-test for unpleasant modulation, increased when the amygdala relative volume was included as covariate. Moreover, together with the upper cluster size, the p-values decreased in the SPM t-test analysis for arousal modulation when the amygdala relative volume was included as a covariate, indicating a more significant difference across groups when including the relative amygdala volume in the analysis.

Taken together, our results point to the key role of the amygdala volume in the MDD and the severity of the symptoms of MDD, and its relationship with the attentional processing of highly emotional pictures in the right superior parietal cortex.

While the present study has found significant differences at the physiological level (functional and morphological), the statistical analysis revealed no significant differences across experimental groups: neither MDD nor the family history of MDD (see table 3, appendix). These results are controversial because we find inconsistent results concerning the behavioral differences relying on depression (Henrriques and Davidson, 2000; Rottenberg et al., 2005). However, the significant differences across experimental conditions within each experimental group support the subjective differences across conditions at both valence and arousal levels (see table 1 and 2, appendix), highlighting that whereas individuals' subjective experience of emotional and neutral stimuli appears to be the same regarding to the behavioral level, the psychophysiological performance differs from each experimental group.

To summarize, despite the not perfect fitting results to our prior hypotheses, the results provided by this work proofs the difference in the attentional brain network in presence of MDD and FH, and its interaction. Moreover, we found differences at the autonomic level evidenced by the differences in the HR change regarding to the MDD, highlighting the general attenuated response related to the current status of MDD. Despite the lack of differences regarding the FH at the autonomic and volumetric levels, we found a strong

correlation between HR change and the parietal enhanced ssVEF amplitude during orienting response independently from the experimental factors. Finally, we found enhanced size and significance within the right parietal cortex related to the relative amygdala volume, emphasizing the predominant role of the amygdala in the attentional processing during MDD.

6.1. Limitations of the current study and further research directions

As discussed in the discussion section of previous chapters, the current study has incurred some experimental limitations that should be considered for future research in the field:

There is a mismatch between the functional (cardiac and biomagnetic) sample and the structural sample size at the sample level. That is due to the high experimental death toll due to the low adherence of MDD patients to assist to the MRI recording after previous MEG recording and clinical evaluation. However, we understand the impairment that anhedonian syndromes involve, and we are more than thankful to all the individuals composing the experimental sample, even more to those suffering from MDD clinical symptoms.

At a methodological level, the frequency implemented in the steady-state paradigm, modulated at 10 Hz, could probably interact with alpha rhythm, making it impossible to estimate the eventual alpha variations between experimental groups. Future planned experimental paradigms will focus on higher frequencies in order to avoid alpha-band rhythm.

Concerning the heart rate change analysis, as previously mentioned in the discussion section, in the recent publication of our group (Echegaray and Moratti, 2021), we emphasize the different cardiac activation patterns, where subjects performed accelerative or decelerative cardiac responses. We aim to analyze current heart rate data in terms of acceleration/deceleration and analyze the eventual premotor response at the cortical level associated with this activation pattern.

Finally, regarding the behavioral level (where no significant differences were found across experimental group), an interesting approach to deeper understand and highlight the physiological differences across experimental groups would be to correlate the behavioral response for each concrete stimulus with its concrete physiological response. This could improve our understanding of the eventual relationship between the physiology and the subjective experience in emotional processing.

6.2. Conclusions:

The present study was born with the aim of understanding the impact of the family history of depression and the depression itself on the attentional processing of emotional stimuli. Concretely, considering the right temporo-parietal cortex as a key point in the characterization of a functional endophenotype of the unipolar major depressive disorder: regarding this point, this study failed.

Unfortunately for our hypotheses, the results did not show any significant difference in the arousal regulation in the right temporo-parietal cortex. However, this study has identified the critical role of the right superior parietal cortex, not only in the current depression status but in the presence of familial load of depression. Moreover, our results point to an unbalanced activation pattern in the fronto-parietal attentional network, characterized by the down-regulation of the right middle frontal gyrus and the over-reactivity of the right superior parietal cortex to highly-arousing emotional images. Given the inhibitory character of the right frontal cortex, the up-regulation of the attentional processing, evidenced by the increased right parietal activity, could represent the consequence of the down-regulation of the right middle frontal gyrus. Nevertheless, our results are not strong enough to support this hypothesis, and therefore, more research focused to this fronto-parietal relationship is needed. However, our results point to a disrupted attentional performance of the right fronto-parietal network, more than an isolated dysfunctional region.

Another unexpected but highly relevant result is the absence of significant differences within the depressed sample regarding the family history of depression. At this point, we speculate about the systemic failure of the whole network under current depressive status, making hinder the possibility of finding effects of an endophenotype further than the predisposition of the risk factor: it is not possible to appreciate the hypo-function of a system that is already not able to work.

This speculative idea is supported by the differences found in the right fronto-parietal network regarding the MDD itself, where the depressed patients exhibited a decreased performance of this network during the arousal modulation.

A satisfactory item of the current study has been the consistent results found regarding the impaired performance of this network in the depression itself, pointing to a well-characterized dysfunction within the depression under a motivated-attention framework.

Regarding the heart rate change differences as a function of the current depressive status, our results offer robust support to the blunted response under major depressive disorder. This point is crucial not only by the science but also for the future of pharmacological, cognitive, and behavioral therapy, understanding the effects of this sadly common disorder under a broader physiological framework.

Beyond, with respect to the related cardiac and cortical activity, our data analysis also supports the attentional character of the orienting response, associated with the correlated cardiac deceleration during the second time window and the superior parietal steady-state response.

Regarding the volumetry, the differences in the amygdalar bodies' relative volume as a function of the current depressive status had shed supporting evidence to the previous work, pointing to the larger amygdala volume under current depressive status in the presence of pharmacological drug treatment.

Further, the increased significance in the comparison of MDD and healthy individuals as a product of the amygdala volume covariate illustrates the key role of the amygdala in the attentional processing in MDD. Beyond, the systematic appearance of the superior parietal cortex in the current study, highlights the critical role of the superior parietal cortex in the attentional processing of emotional high-arousing stimuli, and, therefore, its crucial position in the understanding of the impaired emotional processing in psychological disorders, such as major depressive disorder.

Finally, the lack of significant differences in the amygdala volume as a product of the family history of depression is here interpreted as a prove of the dynamic and adaptive character of the amygdala and its eventual link with pharmachological treatments previously discussed in chapter 5. At the same time, this null-result leads the research to focus on different structures, such as the fronto-parietal network, in the characterization and better understanding of an eventual endophenotype of the depression, for a further improvement of individuals suffering from depression.

Appendix I: HDRS and HARS

Questionnaires:

As previously pointed out in the methods section, the categorization of the sample across the different experimental groups according to the main independent variables to test in the present study (MDD and Family History of MDD) where tested *a priori* for each participant by a pool of questionnaires as a complement of the DSM-IV semi-structured interview, concretely the Hamilton Anxiety Rating Scale (HARS) and the Hamilton Depression Rating Scale (HDRS). Even when accuracy of both rating scales have been widely described in clinical psychology literature, few is known about the implications of the family history of depression on the scores obtained with a representative sample for these questionnaires.

Results:

Regarding to the independent variable MDD, we found significant differences between both groups in for both questionnaires: HARS ($p=.000$; $\eta^2=.261$); HDRS ($p=.000$; $\eta^2=.632$). As expected, HDRS showed a high sensitivity to discriminate between groups. On the other hand, even when the signification value is high, the size effect of HARS where very low ($\eta^2=.261$), which indicates a weak reliability of this difference.

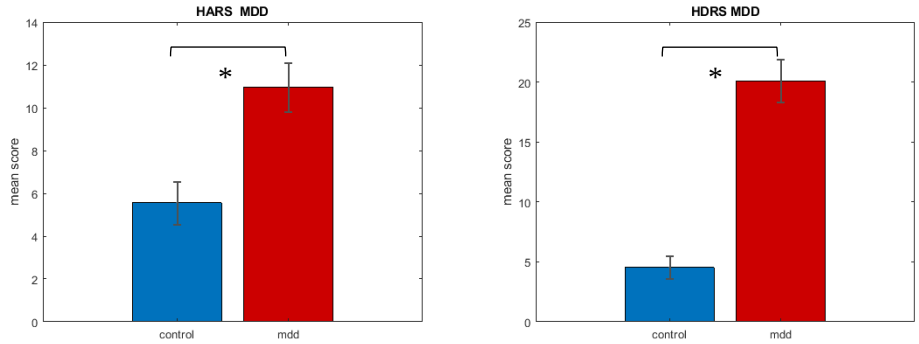


Figure 1 illustrates the mean and standard error associated to the Hamilton Anxiety Rating Scale in the left and the Hamilton Depression Rating Scale in the right. Control group is represented in blue while MDD group is

Attending to the independent variable FH, we found significant differences only for the HDRS ($p=.029$, $\eta^2=.069$) but not for the HARS scale. Nonetheless, we again appreciate a week size effect of this difference.

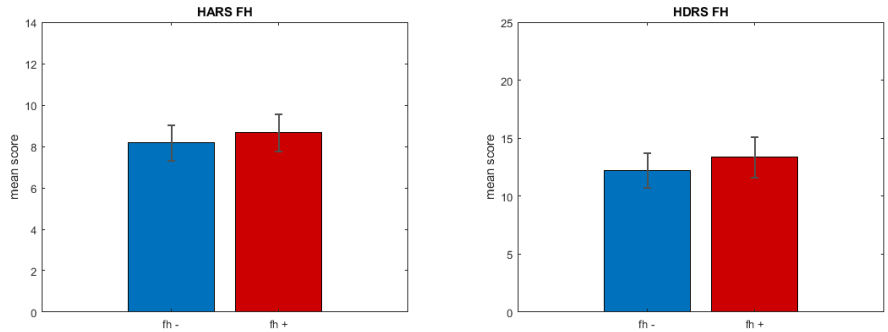


Figure 2 illustrates the mean and standard error associated to the Hamilton Anxiety Rating Scale in the left and the Hamilton Depression Rating Scale in the right. FH- group is represented in blue while FH+ group is represented in red. * indicates the significant differences < .05.

Regarding to the interaction effect for the variables MDD*FH, even when we appreciate a linear tendency of the HDRS, we find only interaction significant interaction effect for the HARS questionnaire (p=.038; η^2=.059). Despite the significance levels of p value, we find again a low value of η^2.

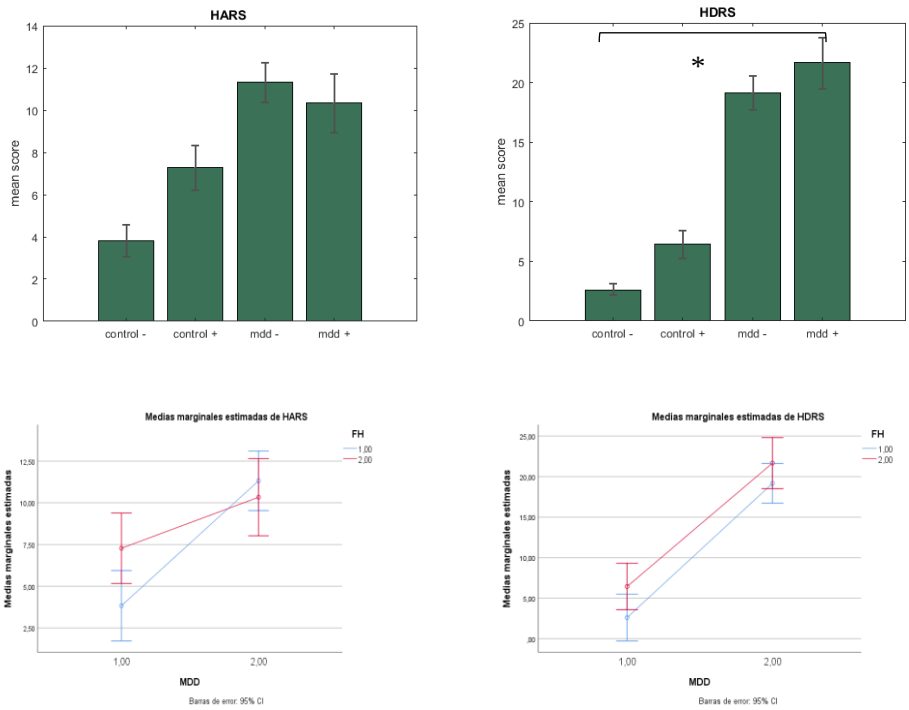


Figure 3.a and figure 3.b illustrate the mean and standard error associated to the Hamilton Anxiety Rating Scale the Hamilton Depression Rating Scale respectively. X ax shows four experimental groups resulting from the MDD and the familiar history of MFF. Figures 3.c and 3.d illustrate the interaction between both factors. * indicates the significant differences < .05.

Appendix II: SAM ratings

Table 1
SAM ratings

	Valence				Arousal			
	Control	MDD	FH-	FH+	Control	MDD	FH-	FH+
Pleasant	7.25 (0.95)	7.34 (0.90)	7.17 (0.93)	7.17 (0.95)	5.51 (1.44)	5.48 (1.55)	5.74 (1.53)	5.37 (1.25)
Neutral	5.23 (0.32)	5.28 (0.43)	5.32 (0.42)	5.20 (0.31)	4.52 (1.11)	4.15 (1.30)	4.52 (1.14)	4.54 (0.87)
Unpleasant	2.03 (0.48)	2.01 (0.73)	2.09 (0.70)	2.08 (0.52)	7.45 (1.31)	7.27 (1.31)	7.46 (1.29)	7.07 (1.56)
Pleasant – Neutral	1.69 (1.76)	2.05 (0.88)	1.66 (1.45)	1.78 (1.56)	1.00 (1.50)	1.04 (2.04)	1.22 (1.98)	0.84 (1.33)
Unpleasant – Neutral	-3.04 (0.86)	-3.26 (0.98)	-3.23 (0.93)	-3.10 (0.70)	2.92 (1.77)	3.12 (1.77)	2.93 (1.66)	2.52 (1.74)

Note. Mean values for each experimental group per condition for valence & arousal. Standard deviations are given in parentheses.

Table 2
SAM ratings

	Valence				Arousal			
	Control	MDD	FH-	FH+	Control	MDD	FH-	FH+
Pleasant vs. Neutral	-13.33 (0.70)*	-14.78 (070)*	-10.95 (0.72)*	-10.64 (0.70)*	-3.54 (1.28)*	-4.14 (1.43)*	-3.83 (1.34)*	-2.96 (1.07)*
Unpleasant vs. Neutral	37.54 (0.56)*	02.89 (0.98)*	21.19 (0.92)*	24.18 (0.70)*	-10.94 (1.77)*	-10.94 (1.77)*	-10.70 (1.66)*	-7.92 (1.74)*
Pleasant vs. Unpleasant	32.29 (0.74)*	24.51 (0.82)*	26.05 (0.82)*	25.47 (0.76)*	-6.52 (1.38)*	-5.55 (1.44)*	-5.18 (1.42)*	-4.57 (1.42)*

Note. . *t*-values from t-test across experimental conditions within groups. *$p < .001$. Standard deviations are given in parentheses.

Table 3

SAM *t-tests*

	Valence		Arousal	
	Control vs. MDD	FH- vs. FH+	Control vs. MDD	FH- vs. FH+
Pleasant	0.39 (0.92) | 0.691	0.03 (0.94) | 0.973	0.07 (1.50) | 0.941	1.02 (1.41) | 0.308
Neutral	0.60 (0.38) | 0.543	1.18 (0.37) | 0.239	1.39 (1.20) | 0.165	0.05 (1.03) | 0.953
Unpleasant	0.16 (0.61) | 0.870	0.08 (0.63) | 0.933	0.61 (1.31) | 0.542	1.11 (1.42) | 0.267
Pleasant – Neutral	1.16 (1.41) | 0.246	0.32 (1.50) | 0.744	0.81 (1.79) | 0.420	0.88 (1.72) | 0.381
Unpleasant – Neutral	1.11 (0.92) | 0.269	0.64 (0.84) | 0.519	0.49 (1.77) | 0.335	0.97 (1.70) | 0.335

Note. *t*-values from t-test across experimental groups for each experimental condition followed by p-value. *$p < .05$ | **$p < .01$. Standard deviations are given in parentheses.

Appendix III: Heart Rate Change Stats

Table 4

Hear Rate Change: Control Group

	1st time window			2nd time window			3rd time window		
	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant
Pleasant		1.004 (.320)	1.91 (.061)		.111 (0.911)	2.655 (.010)*		.849 (.399)	.550 (.584)
Neutral	1.004 (.320)		.954 (.344)	.111 (0.911)		2.397 (.020)*	.849 (.399)		1.146 (.257)
Unpleasant	1.91 (.061)	.954 (.344)		2.655 (.010)*	2.397 (.020)*		.550 (.584)	1.146 (.257)	

Note. *p* values noted in brackets. * < .05. DF = 47.

Table 5

Hear Rate Change: MDD Group

	1st time window			2nd time window			3rd time window		
	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant
Pleasant		.225 (.823)	1.966 (.057)		.921 (.363)	2.107 (.042)*		.471 (.640)	.843 (.404)
Neutral	.225 (.823)		1.968 (.057)	.921 (.363)		1.298 (.203)	.471 (.640)		1.0157 (.255)
Unpleasant	1.968 (.057)	1.966 (.057)		2.107 (.042)*	1.298 (.203)		.843 (.404)	1.157 (.255)	

Note. *p* values noted in brackets. * < .05. DF = 34.

Table 6.

Hear Rate Change: Control vs. MDD Group

	1st time window		2nd time window		3rd time window	
	pleasant - neutral	unpleasant - neutral	pleasant - neutral	unpleasant - neutral	pleasant - neutral	unpleasant - neutral
Control vs. MDD	.542 (.589)	.776 (.239)	.593 (.554)	1.745 (.039)*	.176 (.860)	1.65 (.046)*

Note. *p* values noted in brackets. * < .05. DF = 81.

Appendix IV: Heart Rate Change and Steady-state Correlations Stats

Table 7.

Heart Rate Change / steady-state regression: Unpleasant - Neutral

	Control vs. MDD			FH- vs. FH+			Interaction		
	t-value	p-value	DF	t-value	p-value	DF	F-value	p-value	DF
Second time-window									
- Superior parietal:	.2	.657	64	1.74	.191	64	2.62	.059	64
- Right occipital:	0	.987	70	.56	.456	70	.79	.502	70
Third time-window									
- Right occipital:	2.99	.088	70	.01	.922	70	1.12	.436	70

Note. *$p < .05$ | **$p < .01$.

Table 8.

Heart Rate Change / steady-state regression: Pleasant - Neutral

	Control vs. MDD			FH- vs. FH+			Interaction		
	t-value	p-value	DF	t-value	p-value	DF	F-value	p-value	DF
Second time-window									
- Left parietal:	.19	.661	69	1.82	.182	69	.8	.501	69
- Right parietal:	1.33	.253	69	1.87	.175	69	1.13	.344	69
Third time-window									
- Left parietal:	.34	.560	70	.08	.777	70	.42	.737	70

Note. *$p < .05$ | **$p < .01$.

Appendix V: Amygdala Stats.

Table 9.

Amygdala Stats.

	Control vs. MDD			FH- vs. FH+			Interaction		
	t-value	p-value	DF	t-value	p-value	DF	F-value	p-value	DF
Left Amygdala	2.337	.028	22	.291	.773	22	.26	.617	23
Right Amygdala	2.219	.037	22	.193	.848	22	3.11	.092	23
Bilateral Amygdala	2.409	.024	22	.249	.805	22	1.23	.280	23

Note. *$p < .05$ | **$p < .01$.

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