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AFFECT AND COGNITION IN DEPRESSION: AN RDoC PSYCHOPHYSIOLOGICAL PERSPECTIVE

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To my mom

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OVERVIEW AND AIMS

Depression is among the most common and burdensome conditions experienced worldwide. The development of preventative treatments for depression is partly hindered by an inadequate understanding of the underlying mechanisms involved in its onset and maintenance. Recently, to better understand mechanisms underlying psychopathological conditions researchers are beginning to examine dimensions of functioning rather than diagnostic categories that include heterogenous clusters of symptoms. A dimensional framework is provided by the Research Domain Criteria (RDoC) project, which aims at linking biological and physiological mechanisms to clinical phenomena to generate empirically derived, psychobiological markers of psychopathology. Although depression is increasingly being linked with every RDoC domain, some of them have unique relevance in understanding this condition. Firstly, anhedonia, a core symptom of depression, is linked to the hypoactivation of the approach-related motivational system, which is reflected in the **Positive Valence System** (PVS) of the RDoC. A promising line of research has linked low PVS functioning (i.e., reduced reactivity to pleasant/rewarding cues) with the development of depression. Secondly, recent evidence suggests that depression is linked to reduced reactivity to unpleasant and threatening stimuli, indicating a reduced functioning of the **Negative Valence System** (NVS) of the RDoC. Finally, in addition to affective symptoms, reduced cognitive control, which can be considered within the **Cognitive Systems** of the RDoC, has been widely reported in individuals with depression. However, although some studies reported reduced cognitive control in affective contexts, it remains unclear how the PVS and NVS interact with the Cognitive Systems in depression.

In the "RDoC era", psychophysiological models have an important role in the reconceptualization of mental disorders and their vulnerability. Indeed, psychophysiological studies have highly contributed to the development and refinement of each RDoC dimension

for numerous psychopathological conditions. Psychophysiological models cover multiple levels of analysis of RDoC constructs. This dissertation explored the PVS, NVS, and Cognitive Systems of the RDoC in subclinical and clinical depression using a psychophysiological approach.

Study 1 aimed at simultaneously examining electrocortical correlates of affective disposition and cognitive processing during the viewing of pleasant, neutral, and unpleasant images in a group of young adults with **dysphoria** (i.e., subclinical depression) relative to a control group. The Late Positive Potential (LPP) was examined as a measure of sustained processing of motivationally salient stimuli. In addition, Study 1 employed advanced **time-frequency** analyses of electroencephalographic (EEG) data that allowed disentangling the brain's parallel processing of information, namely affective and cognitive processing of emotional stimuli. Particularly, time-frequency event-related changes were examined, whereby affective disposition was indexed by delta and alpha power, while theta power was employed as a correlate of cognitive elaboration of the stimuli. Cluster-based statistics revealed reduced LPP to pleasant and neutral images in dysphoria relative to the control group. In addition, a centro-parietal reduction in delta power emerged for pleasant stimuli in individuals with dysphoria than controls. Also, dysphoria was characterized by an early fronto-central increase in theta power for unpleasant stimuli relative to neutral and pleasant. Instead, controls were characterized by a late fronto-central and occipital reduction in theta power for unpleasant stimuli relative to neutral and pleasant. The present study granted novel insights into the interrelated facets of affective elaboration in dysphoria, mainly characterized by a hypoactivation of the approach-related motivational system and a sustained facilitated cognitive processing of unpleasant stimuli. In terms of the RDoC dimensions, these results suggest a reduced functioning of the PVS as well as a potential interaction between the NVS and the Cognitive Systems in conferring depression risk. Regarding PVS functioning, further

path model analyses showed that the observed reduced time-frequency delta power to pleasant images in dysphoria is mediated by anhedonia symptoms. These results further support the hypothesis that delta activity reflects the activation of approach motivation.

Study 2 aimed at extending the findings on the PVS in a group of adults with clinical depression. Particularly, the present study aimed at analyzing time-frequency delta power in **full-blown clinical depression** during the viewing of pleasant and neutral pictures and at investigating whether the combination of time-domain (LPP) and time-frequency delta would explain additional variance in the depression status. The LPP of this sample was previously computed and reported, and participants with depression showed reduced LPP to pleasant images relative to controls. Cluster-based statistics revealed a centro-parietal increase in delta power to pleasant relative to neutral pictures in the control group but not within the depression group. Moreover, a fronto-centro-parietal reduction in delta power to pleasant pictures emerged in depression relative to controls. Both a smaller LPP and delta power to pleasant pictures were independently related to depression status. These data suggest that delta power might be a promising electrocortical correlate of reduced approach-related motivation and PVS functioning in clinical depression. Additionally, a blunted delta and LPP might reflect unique processes related to clinical depression and a combination of these measures can be leveraged together to enhance clinical utility.

Study 3 aimed at exploring whether and how the **PVS and NVS influence** the ability to exert **cognitive control** in individuals with depressive symptoms. In this study, a non-emotional ("*cold*") and emotional ("*hot*") task-switching paradigm has been designed to investigate whether individuals with greater depressive symptoms show a general cognitive control difficulty or a specific deficit in affective conditions. This was a behavioral study conducted online during the pandemic and participants ($N = 82$ young adults) were not divided into groups based on their depressive state, but depressive symptoms were considered along a

continuum. Depressive symptoms were linked to greater difficulties in exerting cognitive control in complex situations (mixed-task blocks) compared to simple and semiautomatic situations (single-task blocks) in both task versions. Moreover, greater depressive symptoms were associated with longer latencies in the emotional version of the task across all trial types. Thus, the emotion-specific effect was not modulated by the degree of cognitive control required to perform the task and was also not influenced by the emotional category (pleasant, unpleasant). In sum, depressive symptoms were characterized by a general difficulty to exert cognitive control in both emotional and non-emotional contexts and by greater difficulty in even simple attentional processing of emotional material. This study granted novel insights into the extent of Cognitive Systems functioning and the influence of affective domains (PVS and NVS).

Together, by employing distinct EEG and behavioral measures to tackle several RDoC domains, these studies extend our knowledge of mechanisms linked to depression and its vulnerability, indicating that dysfunctions in multiple RDoC dimensions are involved in subclinical and clinical depression. Ultimately, these findings may contribute to an improved ability to identify and prevent this often chronic and burdensome condition.

Keywords: Depression; Research Domain Criteria; EEG; time-frequency

PART I:

Theoretical background

CHAPTER I

AFFECT AND COGNITION IN DEPRESSION

1.1 Depression: Definition and Epidemiology

Major depressive disorder (MDD) is a mood disorder that affects psychological and physiological functioning causing an elevated functional impairment and represents a leading cause of disease burden worldwide (WHO, 2017). MDD represents the world's most prevalent and burdensome form of psychopathology (Kessler & Bromet, 2013). The World Health Organization estimated that in 2015 about 4.4% of the population was affected by MDD (WHO, 2017), while in Italy, about 10% of the population has experienced at least one depressive episode in their lifetime (Battaglia et al., 2004). During the COVID-19 pandemic, a prevalence of 25% of depression was estimated, highlighting the need to further address this mental health crisis (Bueno-Notivol et al., 2021). Notably, there are important gender differences in the prevalence of MDD, whereby women are two times more likely to develop the disorder compared to men and this discrepancy is stable across different areas of the world (Figure 1.1).

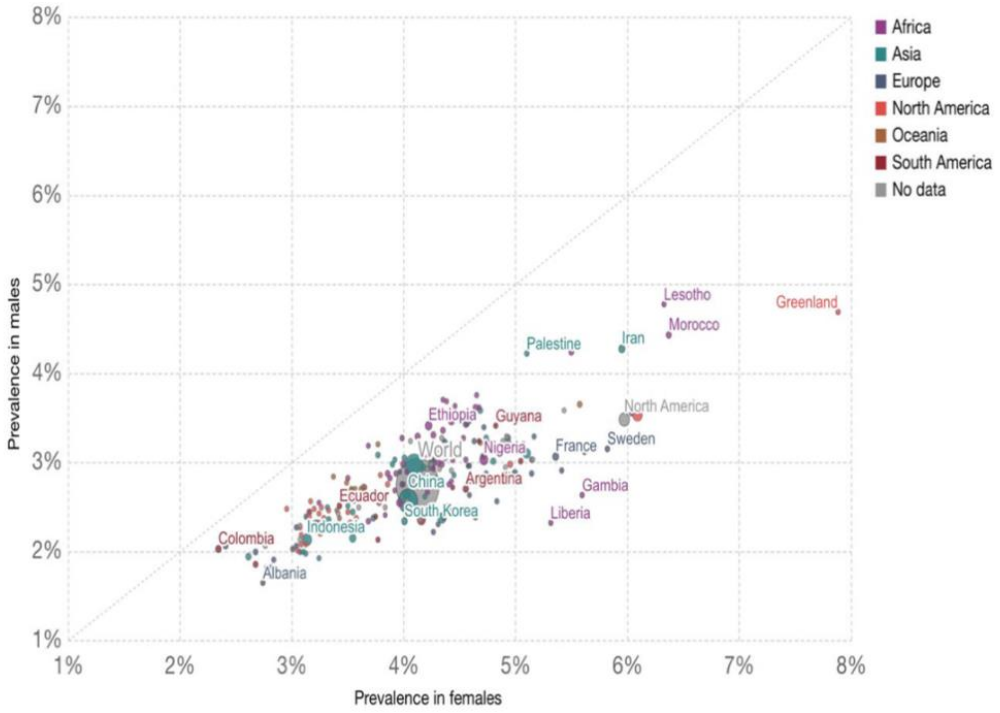

Figure 1.1. Prevalence of depression based on gender across different countries of the world recorded between 1990 and 2017. The representation was based on data from the Institute for Health Metrics and Evaluation e del Global Burden of Disease Study (Our World in Data, 2017).

Depression severely affects both psychological and physiological functioning and was defined as a leading cause of disease burden worldwide in 2010, with an increase of 37.5% as compared to 1990 (Ferrari et al., 2013). Today, depression remains the leading cause of disability globally (WHO, 2017). Notably, MDD is a highly recurrent condition, and each depressive episode severely increases the likelihood that individuals will develop a subsequent episode (Solomon et al., 2000). Indeed, up to 35% of individuals experience a further MDD episode within the first year of recovery (Hardeveld et al., 2010) and the rate of recurrence increases to 85% over the course of the 15 years following recovery (Mueller et al., 1999). Moreover, from a socioeconomic perspective, MDD is among the costliest disorders in Europe, and this makes the study of depression of interest for the entire society (Wittchen et al., 2010).

Given the devastating human and economic toll of depression, numerous researchers have dedicated their careers to developing successful treatments (Gitlin, 2009; Hollon & Dimidjian, 2009). Psychological (e.g., cognitive, behavioral), pharmacological, and neuroscientific (e.g., electroconvulsive therapy, transcranial magnetic stimulation) protocols

(Dimidjian et al., 2011; MacKenzie & Kocovski, 2016; Yadollahpour et al., 2016; Trambaiolli et al., 2021) are often useful to diminish depressive symptoms but many people do not fully recover or do not respond to treatment at all (Cristea et al., 2015; Cuijpers et al., 2010). Given the pervasive nature of MDD and the inconsistent evidence on treatment success, some researchers have focused on the prevention of this disorder, and findings have been promising but rather mixed (Horowitz & Garber, 2006). Efforts to advance effective prevention and treatment strategies might be hindered by our relatively limited understanding of mechanisms implicated in developing and maintaining depression.

Depressive symptoms include depressive mood, anhedonia, appetite changes, sleep disturbances, psychomotor retardation or agitation, lack of energy, excessive guilt and worthlessness, poor concentration, and suicidal thoughts. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), MDD is defined by the presence of five or more of these symptoms, one of which must be a depressed mood or anhedonia causing social or occupational impairment. With these criteria, there are 227 possible combinations of symptoms for an MDD diagnosis (Zimmerman et al., 2015). Therefore, there are numerous pathways and risk factors that lead to the development of depression.

1.1.1 Mapping Depression and its risk onto the Research Domain Criteria[1]

Given the pervasive nature of depression, improving the early identification of depression risk, and developing strategies to prevent the onset of full-blown depression is a core priority (Wahlbeck & Mäkinen, 2008). For prevention efforts to succeed, it is necessary to identify people at risk early and, ideally, before they become ill. Studying individuals who currently have depression prevents assumptions about whether the observed conditions

[1] Part of this section has been written for a review article accepted for publication: **Dell'Acqua C.,** Palomba, D., Patron, E., Messerotti Benvenuti, S. Rethinking the risk for depression using the RDoC: a psychophysiological perspective. *Accepted for publication in Frontiers in Psychology*.

represent mere correlates of depressive states or reliable markers of its risk. Hence, in the field of clinical psychobiology, researchers are shifting their focus to the study of biomarkers that characterize individuals that have a greater risk to develop a full-blown depressive episode. One reliable risk condition is a parental history of MDD: indeed, adolescents with a parental history of depression are 3-5 times more likely to develop depression themselves (Goodman et al., 2011). Other at-risk conditions include individuals with **dysphoria**, a condition characterized by subclinical depressive symptoms. Last, individuals with past depression but currently free from clinical symptoms represent a risk condition of having a recurrence of the disorder (Michelini et al., 2021). These three groups (i.e., parental history of MDD, dysphoria, and past depression) are more vulnerable to the development or recurrence of a full-blown depressive episode than the general population, thus representing target conditions to the study of psychobiological markers of MDD (Hardeveld et al., 2010; Laborde-Lahoz et al., 2015). Some researchers have focused on the prevention of MDD by targeting these at-risk conditions with universal psychological treatments and findings have been promising but rather mixed (e.g., Horowitz & Garber, 2006). Efforts to advance effective prevention and treatment strategies might be hindered by our relatively limited understanding of mechanisms implicated in the development and maintenance of depression.

Considering that the "categorical-polythetic" approach provided by the DSM-5 does not allow a clear identification of at-risk conditions, a viable way to improve our knowledge of the pathophysiological mechanisms linked to depression is to move beyond this view and, instead, adopt a **dimensional approach** (Cuthbert & Insel, 2013; Weinberg, 2023). In this context, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) project, which aims at linking biological and physiological mechanisms to clinical phenomena to generate empirically derived, psychobiological markers of psychopathology (Cuthbert & Insel, 2013; Insel et al., 2010). The RDoC assumes that mental

disorders are multidimensional disorders observable at different levels of analysis (e.g., from genetics to behavior). The RDoC matrix is rooted in a dimensional approach to mental health and includes six domains: Positive Valence Systems, Negative Valence Systems, Arousal/Regulatory Systems, Cognitive Systems, Sensorimotor Systems, and Systems for Social Processes (Figure 1.2). The columns of the matrix include the different units of analysis: genes, molecules, cells, circuits, physiology, behavior, and self-report along dimensional neuro-environmental trajectories. The underlying principle is that by integrating different levels of analysis along these dimensions, the RDoC approach will also contribute to the advancement of our understanding of vulnerability to psychopathology (Dillon et al., 2014). Therefore, RDoC dimensions and constructs should not only be considered as a correlate of psychopathology but also of increased vulnerability. To determine whether dysfunctions within RDoC components relate to future psychopathology, conducting studies based on at-risk categories is warranted.

In the "RDoC era", psychophysiological models have an important role in the reconceptualization of mental disorders and their vulnerability (Shankman & Gorka, 2015; Riesel, Endrass, Weinberg, 2021). Indeed, psychophysiological studies have highly contributed to the development and refinement of each RDoC dimension for numerous psychopathological conditions. Psychophysiological models cover multiple levels of analysis of constructs of the RDoC (e.g., neural, autonomic, and psychological) (Kujawa & Burkhouse, 2017). In the present review, studies that have employed a wide array of psychophysiological measures for the investigation of RDoC dimensions in at-risk samples will be described. Ultimately, this review emphasizes the relevance that psychophysiology is playing in the refinement of the RDoC matrix in the context of depression risk.

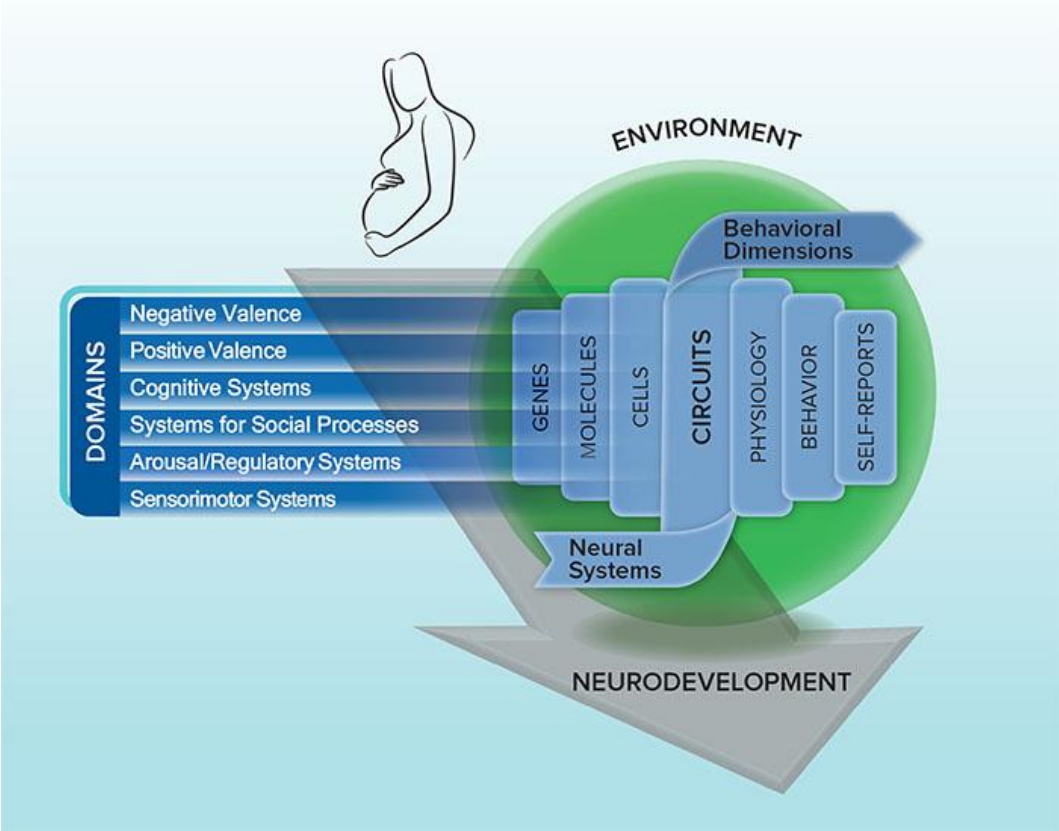

Figure 1.2 Diagram of the RDoC framework. *From www.nimh.nih.gov.*

Examining depression adopting the RDoC lens means trying to understand this condition and its underlying mechanisms in an integrative manner through the examination of multiple units of analysis, spanning, for example, from behavior to neural correlates. Depressive symptomatology can be mapped onto the six domains proposed by the RDoC. As it will become clear, these domains are highly interrelated.

The Positive Valence Systems. Individuals with depression are characterized by low mood and positive emotionality, reduced motivation, and feelings of hopelessness most of the time. Moreover, one of the core symptoms of depression is anhedonia, which can be described as diminished motivation to pursue positive/rewarding outcomes and/or reduced pleasure in response to previously rewarding experiences (American Psychiatric Association, 2013). Individuals with depression show anticipatory anhedonia and this was negatively correlated with the mobilization of extra effort to reach a reward, suggesting that the failure to anticipate

pleasure affects their motivation (Bowyer et al., 2022). In addition, individuals with anhedonia also have difficulties in learning as a function of rewards. Indeed, providing individuals with feedback during the execution of a task usually improves their performance, whereas it does not affect individuals with depression (Ravizza & Delgado, 2014). These symptoms are viewed as impairments in the Positive Valence System (PVS) functioning (Dillon et al., 2014). The PVS is composed of a set of systems involved in anticipating, obtaining, and responding to pleasant or rewarding stimuli (Olino, 2018; Kujawa et al., 2017). Reduced PVS functioning in depression has been evidenced by self-report (McFarland & Klein, 2009; Treadway & Zald, 2011), behavioral (Pizzagalli et al., 2005: Treadway et al., 2012), and electrophysiological (Hajcak Proudfit, 2015; Liu et al., 2014) units of analysis (Nusslock & Alloy, 2017). At the neural level, the processing of appetitive and rewarding stimuli activates a network of cortical and subcortical brain regions, including the ventral tegmental area, nucleus accumbens, and frontostriatal pathways (Craske et al., 2016; Dillon et al., 2014; Nusslock & Alloy, 2017). Functional magnetic resonance imaging (fMRI) studies have shown that individuals with depression had a lower activation of brain regions associated with the PVS during reward tasks as compared to healthy controls (Ng et al., 2019; Pizzagalli, 2014). In addition, blunted electrocortical responses to pleasant and rewarding stimuli have been well documented in depression (e.g., Admon & Pizzagalli, 2015), in individuals at-risk for depression (e.g., Gotlib et al., 2010; Luking et al., 2016), and to prospectively predict the development of depression (e.g., Bress et al., 2013; Nelson et al., 2016). Reduced PVS functioning is one of the main focuses of the current work and psychophysiological measures of reduced approach motivation in depression are illustrated in section 1.2 of this Chapter. Additionally, electrocortical correlates of the PVS functioning and their changes in depression and risk conditions will be thoroughly discussed in Chapter II.

The Negative Valence Systems. The Negative Valence Systems (NVS) encompass five constructs related to responses to aversive stimuli or events. These constructs include responses to acute threat, potential threat, sustained threat, loss, and frustrative non-reward. Compared to the PVS, data on the reactivity to unpleasant stimuli in depression and vulnerability to depression have been extensively produced in several (and different) research areas and therefore the findings are rather mixed and sometimes even unable to show any significant effect (for a meta-analysis and a review on psychophysiological studies on emotional reactivity see Bylsma et al., 2008 and Bylsma, 2021). Initial theories suggested that depression would be characterized by an increased reactivity to unpleasant emotional stimuli based on the idea that individuals' background affective state would prime reactivity to a stimulus of matching valence (Rosenberg, 1998; Rottenberg, 2017). Cognitive theories of depression (Beck & Bredemeier, 2016) seem to have a similar hypothesis: negative cognitive schemas guide preferential processing of negative stimuli which, in turn, lead to enhanced attention and intake of these cues. For instance, in support of this claim, individuals with dysphoria, but not controls, repeatedly showed a prolonged cardiac deceleration during passive viewing of unpleasant stimuli as compared with neutral ones, suggesting a sustained intake of unpleasant cues and a mood-related bias in this at-risk group (Messerotti Benvenuti et al., 2020; Moretta et al., 2021). However, the greater processing of unpleasant images observed in dysphoria does not seem to lead to greater action preparation and reactivity. Indeed, from most research using both passive and active tasks and different psychophysiological measures, depression appears to be mostly characterized by a reduced emotional reactivity to unpleasant stimuli (Foti et al., 2010; Hill et al., 2019; MacNamara et al., 2016; for a review see Bylsma, 2021). The lack of reactivity to unpleasant contents is in line with the **emotion context insensitivity hypothesis** (ECI; Bylsma et al., 2008; Bylsma, 2021; Rottenberg et al., 2005; this model will be better described later in this Chapter in Section 1.2), which suggests that

depression might be characterized by an overall blunted emotional reactivity, with reduced psychophysiological responses to all affective cues.

In support of the ECI model in depression, a few psychophysiological studies reported a greater electrocortical activity to unpleasant images in depression (Auerbach et al., 2015; Burkhouse et al., 2017; Zhang et al., 2016), while others reported reduced electrocortical reactivity to negative stimuli in individuals with clinical depression (Foti et al., 2010; Hill et al., 2019; MacNamara et al., 2016) and subclinical depression (Benning & Oumeziane, 2017; Grunewald et al., 2019). Specific psychophysiological correlates of NVS functioning in depression are illustrated in Section 1.2.3 of this Chapter, while electrocortical correlates are described in Chapter II.

The Arousal and Regulatory Systems. The DSM-5 criteria for MDD include physical alterations, such as fatigue, sleep disturbances, and appetite changes. Beyond these three bodily symptoms, no other physical symptom is mentioned. However, other somatic symptoms are prevalent in individuals with depression, including headaches, musculoskeletal symptoms, palpitations, and upset stomach (Breslau et al., 2000; Vaccarino et al., 2008). Arousal might have a primary role in the somatic and neurovegetative symptoms experienced by individuals with depression and they can be ascribable to the Arousal and Regulatory Systems (ARS) of the RDoC (Gunzler et al., 2020). Somatic symptoms of depression are associated with longer disease duration, greater disability, poorer clinical outcomes, and elevated healthcare costs (Vaccarino et al., 2008). These somatic consequences could partly be due to metabolic, immuno-inflammatory, autonomic, and hypothalamic-pituitary-adrenal axis (HPA) imbalances which can also reflect an altered psychoneuroimmunological interaction. These imbalances are often present among MDD patients (Penninx et al., 2013) and they can increase

the risk of developing cardiovascular diseases, metabolic syndromes, and overall immune system deterioration (Wolkowitz et al., 2011).

Depression has been related to autonomic imbalances, such as increased heart rate and reduced heart rate variability (HRV), a measure of beat-to-beat variation in the heart over time that reflects the balance between the two autonomic nervous system (ANS) branches on the heart, in resting conditions (Dell'Acqua et al., 2020; Koch et al., 2019). These patterns of reduced HRV in a wide array of at-risk samples suggest that decreased cardiac autonomic balance might serve as an early marker of depression vulnerability (Figure 1.3). Furthermore, meta-analytic evidence suggested that, during a stressor, individuals with depressive symptoms showed hypo-reactivity as indexed by lower fluctuation in heart rate and HRV (Schiweck et al., 2019).

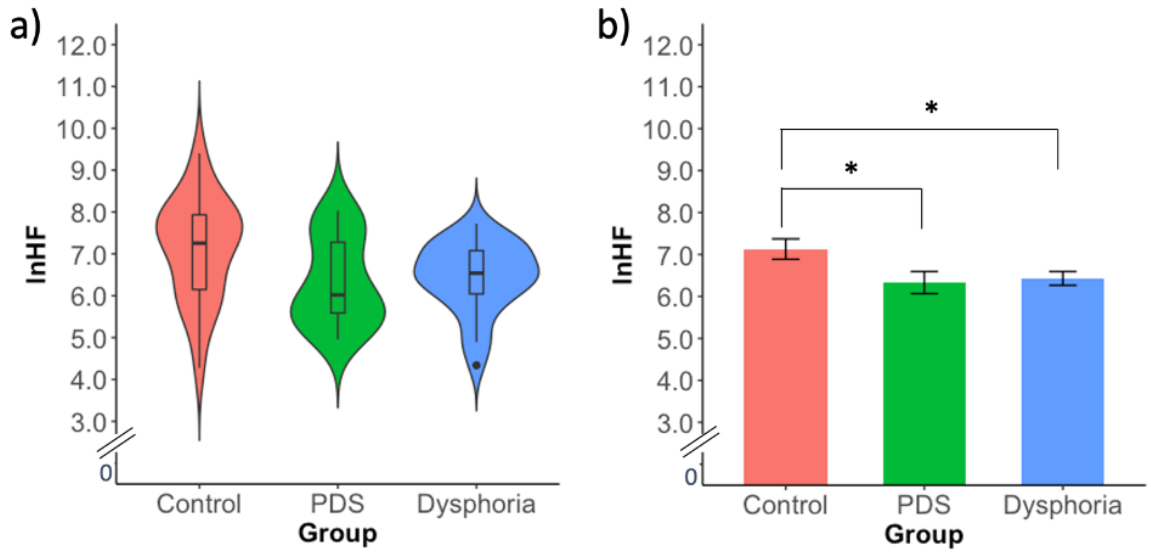

Figure 1.3 Violin plot of the distribution of high frequency (lnHF) HRV values, that reflect cardiac vagal tone, at rest for controls, individuals with past depression (PDS) and with dysphoria. The plot shows the median (indicated by the black horizontal band), the first through the third interquartile range (the vertical band), and estimator of the density (thin vertical curves) of the lnHF in each group (comparable to a boxplot, except that the distribution of the variable is illustrated as density curves). The violin plot outlines illustrate kernel probability density, that is the width of the shaded area represents the proportion of the data located there. Panel b) Mean lnHF values for the three groups (control, PDS and dysphoria). Error bars represent ± standard error of the mean (SEM). *$p < .05$. Notes: PDS= past depressive symptoms. *From Dell'Acqua, Dal Bò et al., 2020.*

Another psychophysiological measure related to autonomic activity is skin conductance. As previously described, skin conductance mirrors exclusively the sympathetic nervous system activity. Accordingly, during the viewing of pleasant and unpleasant pictures, healthy individuals showed comparable skin conductance responses to similarly arousing stimuli, both pleasant and unpleasant, relative to neutral ones. Instead, individuals with subclinical depression showed reduced skin conductance to all emotional stimuli, supporting both the hypothesis of reduced functioning of the Arousal and Regulatory Systems and of the PVS and NVS domains (Benning & Oumeziane, 2017). Similarly, reduced skin conductance response was reported in individuals with depression during a mental arithmetic task (Kim et al., 2019, Figure 1.4) and in individuals with dysphoria during a public speaking task (Schwerdtfeger & Rosenkaimer, 2011). Additionally, even unaffected offspring of chronically depressed mothers showed reduced skin conductance to stressful situations (Cummings et al., 2007).

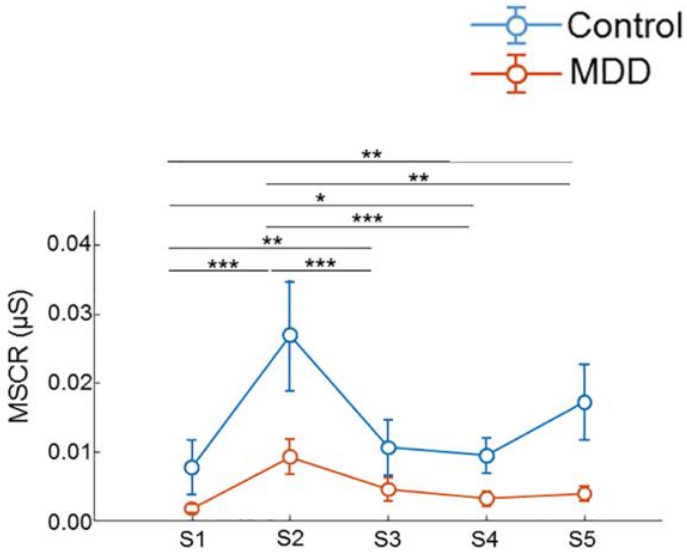

Figure 1.4 Reduced skin conductance response (MSCR) in individuals with depression (MDD, red line) relative to controls (blue line), during baseline (S1), a mental arithmetic task (S2), recovery (S3, S5), and relaxation (S4). *Adapted from Kim et al., 2019.*

Another measure related to the Arousal and Regulatory domain is cortisol, the main stress hormone that reflects HPA functioning and that has been widely used in the study of

neuroendocrine and dysfunctions in MDD (Herbert, 2013; Lopez-Duran et al., 2009). Individuals with depression have been shown to have elevated morning cortisol (e.g., Michael et al., 2000) and a greater cortisol awakening response (e.g., Bhagwagar et al., 2005; Vreeburg et al., 2009). Moreover, higher cortisol awakening response levels were reported in adolescents who subsequently developed an episode of major depression in the following year (Adam et al., 2010; Vrshek-Schallhorn et al., 2013). Collectively, these findings on morning cortisol and CAR suggest that depression might be related to a hyperactive HPA. Regarding cortisol reactivity to a stressor, a relatively blunted cortisol stress reactivity even when controlling for baseline measures was repeatedly observed in MDD (Burke et al., 2005; Harkness et al., 2011).

Cognitive Systems. In addition to affective and somatic symptoms, cognitive symptoms have been widely reported in individuals with depression. One of the DSM-5 criteria for depression is, indeed, a diminished ability to think, concentrate, or make decisions (APA, 2013). As it will be better described later in this Chapter, cognitive dysfunctions in depression include impairments in cognitive control. Studies have reported that individuals with depression show reduced sustained and divided attention (McClintock et al., 2010), overgeneralized declarative memory (Zhou et al., 2017), reduced cognitive flexibility, set-shifting, planning, and updating (Dotson et al., 2020). These deficits align with the Cognitive Systems domain of the RDoC, which includes constructs of attention, perception, declarative memory, language, cognitive control, and working memory (Cuthbert & Insel, 2013; Insel et al., 2010). At the neural level, some of these processes can be mapped onto frontal brain regions, as described in Section 1.3.2. Besides, impairments in the Cognitive Systems are strictly related to the PVS and NVS domains. For example, according to the impaired disengagement hypothesis (Koster et al., 2011), depression is characterized by difficulty in disengaging attention and impaired attentional control in response to negative thoughts or

events. Moreover, at the neural level, this impaired cognitive regulation of negative emotions is related to a failure to recruit frontal control over the amygdala (Taylor & Fragopanagos, 2005). Regarding electrocortical correlates of cognitive control, individuals with depression show reduced neural indices of monitoring and detection of conflict (e.g., Kaiser et al., 2003; Weinberg et al., 2015; Ruchsow et al., 2004, 2006). However, the psychological and physiological mechanisms that mediate the executive function impairment seen in depressive disorders are still unclear. Interestingly, during an executive control task participants with depression presented reduced HRV relative to controls, indicating that there may be an underlying flexibility dysfunction in depression (Bair et al., 2021; Hoffmann et al., 2017). Indeed, it is possible that blunted sympathetic reactivity and reduced tonic parasympathetic control might provide a suboptimal condition for cognitive performance in depression (Bair et al., 2021). A detailed description of cognitive impairments in depression can be found in Section 1.3 of this Chapter.

The Sensorimotor Systems. Psychomotor disturbances (i.e., retardation or agitation) are core features of depression and are included as a diagnostic criterion in the DSM-5. Psychomotor disturbances are particularly common among individuals with a severe manifestation of MDD (Parker, 2000). These symptoms align with the Sensorimotor Systems of the RDoC, a domain that was recently added to the matrix (Garvey & Cuthbert, 2017). The Sensorimotor domain includes four constructs, namely motor actions, agency and ownership, habit, and innate motor patterns. Psychomotor retardation can be ascribed to the motor actions construct of this dimension. Several neuroscientific studies have shown that MDD's motor symptoms can be mapped on the cerebral motor circuits, showing, for example, increased resting-state perfusion in the motor cortex in individuals with psychomotor retardation (Yin et al., 2018).

Psychomotor retardation in MDD has been documented using self-report measures (Calugi et al., 2011) and actigraphy (Razavi et al., 2011; Shankman et al., 2020; Walther et al., 2019). Interestingly, motor processes included in the Sensorimotor Systems are activated in conjunction with motivational processes described in other domains, such as the PVS (i.e., when positive emotionality drive approach actions; Walther et al., 2019).

EEG correlates of motor activity disturbances have only been investigated in clinical depression and have focused on the examination of resting spectral characteristics in relation to psychomotor retardation levels (Cantisani et al., 2015; Nieber & Schlegel, 1992). For example, a left-lateralized pattern of frontal alpha activity was negatively associated with activity levels (assessed with an actigraphy) in individuals with MDD, suggesting that psychomotor retardation may be related to impaired motivational drive (Cantisani et al., 2015). A negative covariance between resting alpha power over motor areas and activity levels was also reported (Cantisani et al., 2015; Nieber & Schlegel, 1992). Considering that alpha power mirrors inhibition of a cortical region, these results might indicate that psychomotor retardation is reflected in reduced motor cortex activity even in conditions of rest, potentially representing a trait feature or these alternations (Cantisani et al., 2015).

Overall, the exact mechanisms of psychomotor retardation and agitation in depression are still undefined and studying motor processes in depression adopting the RDoC lens could be a promising approach to improve our understanding of this feature of depression (Walther et al., 2018).

The Systems for Social Processes. Depressive symptoms have long been associated with social impairments and poor social functioning (Gotlib & Hammen, 1992). Social impairments are included within the Systems for Social Processes of the RDoC, which are composed by the following domains: Affiliation and Attachment, Social Communication,

Perception and Understanding of Self, and Perception and Understanding of Others. Depression is associated with social anhedonia, namely reduced drive for social affiliation, but also with increased sensitivity to social rejection. Individuals with MDD are characterized by impaired interpersonal (Hirschfeld et al., 2002), marital (Fink & Shapiro, 2013), and work functioning (Kessler et al., 2003). Overall, these social impairments could be related to many factors, such as a deficit in understanding and controlling emotions in social contexts, reduced approach motivation, reduced empathy in social interactions, and a reduced problem-solving ability for interpersonal issues. Overall, integrative research suggested that the interrelation among biological (e.g., genetic, neural), psychological (e.g., emotion regulation and recognition), and environmental factors (e.g., exposure to social stressors) over time may explain the risk of developing MDD (Kupferberg et al., 2016).

As might already be evident, this domain is closely related to the PVS, particularly in the study of depression. Recent studies have shown that individuals with MDD were characterized by reduced sensitivity to social rewards, a process that has been included in the Affiliation and Attachment domain during a social feedback task. For instance, it has been recently observed that reduced neural activity to social rejection during this task significantly predicted the onset of depressive symptoms in a sample of adolescents (Pegg et al., 2019; Pegg et al., 2021) and in individuals with subclinical symptoms (Jin et al., 2019), suggesting that blunted neural sensitivity to being socially excluded might represent a psychobiological marker of MDD. In further support for reduced sensitivity to social affiliation, individuals with dysphoria showed a reduced increase in heart rate to social rewards relative to a control group (Brinkmann et al., 2014).

1.2 Affective Models of Depression

1.2.1 The Appetitive and Defensive Motivational Systems

Although emotion represents an important field in psychology and neighboring disciplines, there is little consensus about its definition and organization. According to some researchers, emotion is conceptualized as being organized around two motivational systems, one appetitive and one defensive, refined throughout evolution to facilitate survival and adaptation to the environment (Bradley et al., 2001; Davidson, 1998; Lang & Bradley, 2013). The defensive/avoidance system is activated in contexts of threat and is associated with defensive and withdrawal behavior in response to aversive stimuli (e.g., attack, illness, injury). The appetitive/approach system is a reward-seeking system activated in contexts that promote survival (sex, ingestion, caregiving) and is associated with behaviors of approach toward pleasant rewarding stimuli. The individual differences in the balance between the two motivational systems have been referred to as the affective style (Davidson et al., 2000; Davidson, 1998). An individual's affective style drives the behavioral and physiological response to emotional stimuli which, in turn, is related to depression and other mental disorders. Indeed, motivational systems modulate perceptual processing, attentional engagement, and energy mobilization toward emotional cues. Particularly, the defensive system is activated in threatening or unpredictable situations and triggers behavioral patterns of fight, flight, or freeze. These behaviors are sustained by neural circuitry that comprises the amygdala, the anterior and medial hypothalamus, and the periaqueductal grey matter (LeDoux, 2000). Moreover, this neural pathway is differentially supported and mediated by the sympathetic and parasympathetic nervous systems. For example, to cope with a threat, the sympathetic nervous system elicits a fight or flight response based on the available resources of the individual. During this process, physiological changes occur, such as changes in cardiovascular activity. Particularly, threatening/unpleasant stimuli prompt increased cardiac

deceleration (Figure 1.5), which reflects the facilitation of intake and perceptual processing during the early stages of the defense response (Bradley et al., 2005; Palomba et al., 1997). Later in the defense response, a shift to cardiac acceleration – which indicates the preparation for action – can occur only when the stimuli are highly fearful and elicit an unusually high level of defensive activation (e.g., phobic stimuli, Klorman et al., 1977). Contrariwise, the heart rate changes in response to an appetitive/rewarding stimulus (e.g., erotic scenes, sports, food) are characterized by an initial deceleration and then by a mid-interval acceleration, which likely reflects a tendency to approach (Bradley et al., 2001). Moreover, the appetitive response primarily activates dopaminergic reward circuits in the brain aimed at reaching rewards. Taken together, the activation of the two motivational systems is associated with a specific behavioral and physiological pattern of responses.

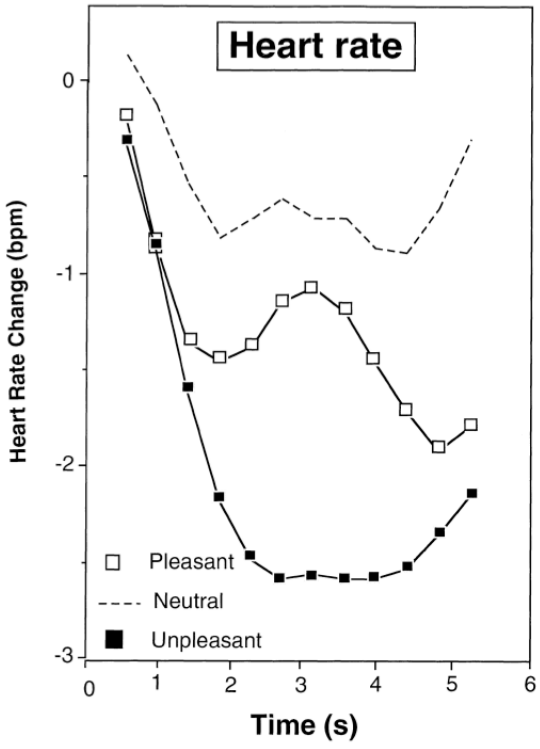

Figure 1.5 Changes in the heart rate while participants viewed pleasant, neutral, and unpleasant pictures. Unpleasant pictures elicit a sustained decelerative response, while pleasant ones induce a triphasic response (deceleration, acceleration, deceleration). *Adapted from Bradley et al., 2001.*

1.2.2 The Dimensional Model of Emotions

The motivational model conceives emotions as action dispositions, representing individuals' readiness to act within their environment accompanied by a physiological preparatory activation (Frijda, 2007; Lang et al., 1998). The relation between emotion and action is evident even in the etymology of emotion, a term that comes from the Latin *ex-movere*, which refers to the concept of moving. In this context, the dimensional model proposed by Lang and colleagues (1998) views emotion as a wide disposition to respond to environmental conditions with expressive language, behavioral patterns, and physiological changes. According to this model, emotion is the final product of the interaction between these three systems. The *subjective system* represents the personal experience of each individual in relation to an emotional stimulus and is usually reported verbally. The *behavioral system* represents the motor sequences in response to the emotional stimulus, including postural and expressive changes as well as actions that imply approach, fight, or avoidance of the stimulus. As described above, the *physiological system* regulates the somato-visceral and central responses to emotionally valenced cues. The role of these three systems in determining an emotional state is well-established in the literature and is still a valid framework nowadays. According to Lang and colleagues, the three systems are partially independent but strictly connected with each other.

Different emotional states can be distinguished based on the direction of the disposition that the stimulus elicits (appetitive vs. defensive) and on the intensity, or strength, of the energy mobilization (Miller, 1966). Direction and intensity are closely linked to two main dimensions that are at the basis of human emotion: valence and arousal (Lang et al., 1997). The dimension of *valence* is fundamental in regulating actions along an approach/withdrawal criterion, based on the (un)pleasantness of stimuli. The dimension of *arousal* reflects the subjective feeling of calmness/activation and reflects the intensity of the physiological response. Lang and

colleagues (1997) have developed the International Affective Picture Processing (IAPS) database, a set of pictures based on their dimensional model of emotions. Their aim was to create a standard database of images that can be used in experimental settings across the world. The set is composed of more than 1000 images of different semantic categories and as shown in Figure 1.6, each one of them has a rating along the dimensions of arousal and valence (Lang, 1997).

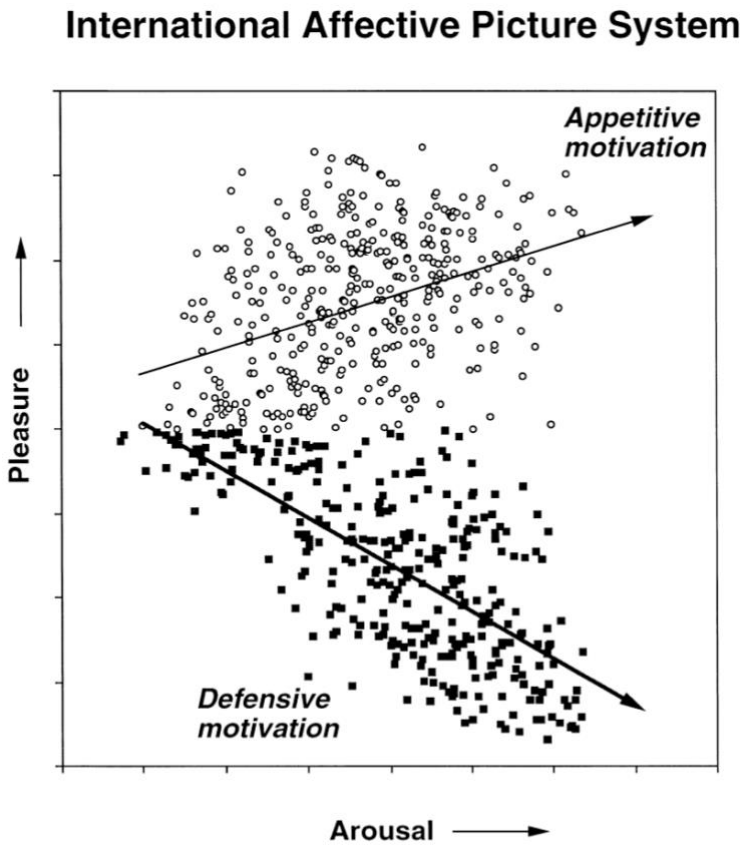

Figure 1.6 Pictures from the International Affective Picture System are distributed along the bi-dimensional space composed of valence (pleasant/unpleasant) and arousal (calm/activated). Each point in the plot represents the ratings for one picture. *From Bradley et al., 2005.*

1.2.3 Emotional Reactivity in Depression

As reviewed above, emotions activate different response systems (subjective, behavioral, and physiological) and the emotional response is associated with individuals' affective style (i.e., individual differences in the activation of the two motivational systems). Variations in affective style are thought to underlie psychopathology and, particularly,

depression. However, the way in which depression relates to specific deficits in emotional reactivity is still unclear. Over the last decades, cognitive theories of depression have sustained that depressed mood is linked to the preferential processing of negative stimuli (Beck, 1987). Drawing from these early cognitive accounts, the first view on emotional reactivity in depression was developed, the **negative potentiation hypothesis**, which holds that pervasive negative mood states that are prevalent in MDD contribute to potentiate emotional responding to unpleasant stimuli, indicating a heightened activation of the withdrawal-related motivation system (Bylsma et al., 2008; Rottenberg et al., 2005). Although this view is in line with Beck's schema model and classic cognitive theories of depression (see Section 1.3), there is very little empirical research that supports it. A further view is the **positive attenuation hypothesis**, which suggests that MDD is associated with reduced emotional reactivity to pleasant stimuli, indicating a blunted activation of the appetitive motivational system. Contrary to the negative potentiation, this view is supported by accumulating empirical evidence (Bylsma et al., 2008; Bylsma, 2021) and is consistent with one of the core symptoms of depression, anhedonia, and other symptoms such as psychomotor retardation, apathy, and fatigue. Since this hypothesis focuses solely on pleasant stimuli, it is compatible with the negative potentiation, namely individuals with depression can show both patterns. However, recent empirical evidence suggests that depression might be characterized by blunted emotional reactivity to all emotional stimuli, regardless of their valence. This has been defined as the **emotion context insensitivity** (ECI) hypothesis (Bylsma et al., 2008; Bylsma, 2021) and indicates that depression is characterized by the hypoactivation of both motivational systems. The ECI is based on evolutionary theories that described depression as the product of environmental disengagement (Bylsma et al., 2008), which is manifested through a decreased appropriateness of responses to both pleasant and unpleasant stimuli. Accumulating and consistent evidence has supported the ECI model: a meta-analysis of 19 studies (Bylsma et al., 2008) demonstrated that individuals

with depression have an overall pattern of emotional disengagement to all emotionally valenced cues across behavioral (e.g., McIvor et al., 2019), self-report (e.g., Benning & Oumeziane, 2017; Kaviani et al., 2004), and physiological (e.g., Benning & Oumeziane, 2017; Sloan & Sandt, 2010) response systems (Bylsma et al., 2008). This blunted emotional reactivity can be conceptualized as a **reduced functioning of the Positive and Negative Valence Systems of the RDoC**.

To date, most of the research in support of the ECI model has focused on emotional reactivity to pleasant and rewarding stimuli. Particularly, numerous neuroimaging and electrophysiological studies have reported reduced neural processing of rewarding and pleasant stimuli, suggesting a reduced behavioral and electrocortical activation of reward anticipation and receipt in MDD (Benning & Oumeziane, 2017; Forbes & Dahl, 2012; Gaillard et al., 2020; Klawohn et al., 2021; Webb et al., 2017). Further information on electrocortical activity in response to emotional stimuli will be described in Chapter II. Although much of the psychophysiological contributions to the study of the PVS in depression vulnerability come from EEG studies, other psychophysiological indices have also been useful in exploring this relation. For example, the startle eyeblink reflex consists of the rapid contraction of the *orbicularis oculi* muscle and represents a measure of affective modulation when the startle probe is presented more than 500 ms after the beginning of the presentation of a stimulus. Specifically, the reflex is potentiated during unpleasant affective states and inhibited during pleasant affective relative to neutral states (e.g., Bradley et al., 1999). The absence of startle attenuation to pleasant images was observed in depression (e.g., Dichter & Tomarken, 2008; see Boecker & Pauli, 2019; Figure 1.7), in dysphoria (Mneimne et al., 2008), and in individuals with past but recurrent depression (Vaidyanathan et al., 2014), and indicates reduced approach motivation.

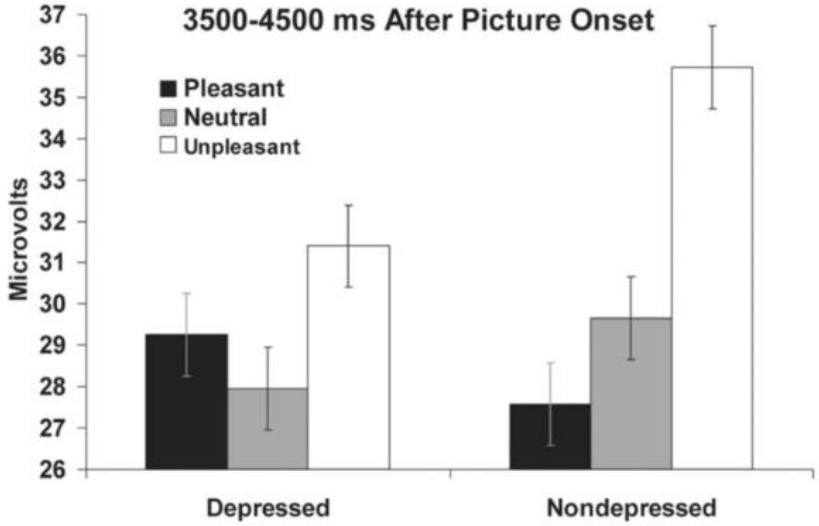

Figure 1.7 Reduced startle modulation in a group of individuals with MDD relative to a control group. *Adapted from Dichter & Tomarken, 2008.*

Moreover, reduced skin conductance levels, a measure that reflects the activity of sympathetic cholinergic neurons at the level of eccrine dermal sweat glands (Venables & Christie, 1980), to pleasant (but also unpleasant) stimuli have been shown in individuals with dysphoria relative to a control group (Benning & Oumeziane, 2017; De Zorzi et al., 2021). A further measure that can inform us about emotional reactivity is cardiac autonomic modulation, as the heart is dually innervated by the two branches of the autonomic nervous systems, heart rate is an index that mirrors both sympathetic (acceleration) and parasympathetic (deceleration) nervous systems (Berntson et al., 1993). Particularly, during the viewing of emotional videos (pleasant and unpleasant), healthy individuals show heart rate acceleration due to cardiac vagal withdrawal (Kreibig, 2010), and this is considered a pattern of autonomic modulation to flexibly respond to stimuli in the environment (Porges, 1997).

Evidence in support of a blunted emotional reactivity to unpleasant stimuli is less definite. The first experiments that led to the conceptualization of the ECI model showed that individuals with depression reported a smaller increase in sadness in response to sad films compared to a control group (Rottenberg et al., 2002). On the contrary, in another study, individuals with MDD reported potentiated daily negative affect compared to controls (Bylsma

et al., 2011). At the physiological level, a few studies reported reduced electrocortical reactivity to negative stimuli in individuals with clinical depression (Foti et al., 2010; Hill et al., 2019; MacNamara et al., 2016) and subclinical depression (Benning & Oumeziane, 2017; Grunewald et al., 2019). Other evidence comes from studies on the startle reflex measured at the *orbicularis oculi* muscle during exposure to emotional cues, which have reported reduced startle potentiation to unpleasant stimuli in individuals with depression (Dichter & Tomarken, 2008; Vaidyanathan et al., 2014; Figure 1.7) and subclinical depression (Messerotti Benvenuti et al., 2020, Figure 1.8) relative to controls, suggesting a reduced activation of the defensive motivational system. Moreover, as described above, a few studies documented reduced skin conductance levels to all emotional stimuli in individuals with subclinical depression relative to a control group (Benning & Oumeziane, 2017).

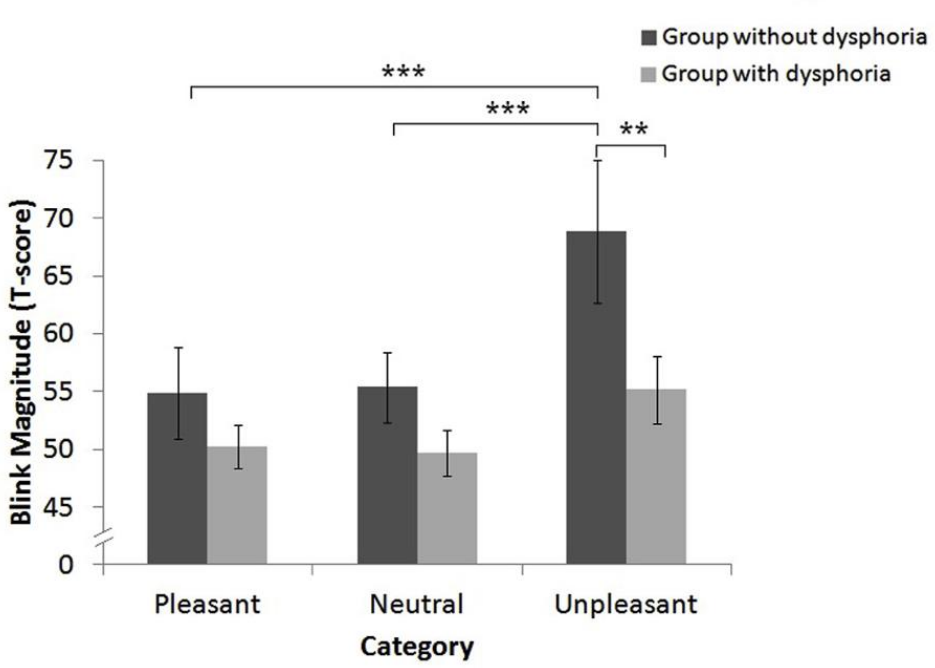

Figure 1.8 Mean blink response magnitude for pleasant, neutral, and unpleasant pictures in a group with dysphoria (i.e., subclinical depression) and in the group without dysphoria. The dysphoria group showed a blunted startle potentiation to unpleasant pictures. *Adapted from Messerotti Benvenuti et al., 2020.*

Another way to examine emotional reactivity to unpleasant stimuli is to assess physiological responses to the commission of an error (i.e., error monitoring). Indeed, making a mistake is generally perceived as subjectively unpleasant and, at times, it can be perilous and

threatening to one's life (Weinberg, Meyer, et al., 2016). For instance, at the physiological level, like other threats, the commission of an error elicits a cascade of defensive responses: greater startle reflex (Hajcak & Foti, 2008), higher skin conductance levels, and slower heart rate (Hajcak et al., 2003; Hajcak et al., 2004). A specific electrocortical measure of error monitoring is the error-related negativity (ERN), an event-related potential (ERP) o the electroencephalographic signal which arises as a negative electrocortical deflection at fronto-central scalp sites within 100 ms following the commission of an error versus a correct response (Gehring et al., 1995). To date, findings on the ERN in depression have been mixed, with studies reporting enhanced (e.g., Chiu, & Deldin, 2007; Holmes, & Pizzagalli, 2010) and reduced (e.g., Dell'Acqua, Hajcak, et al., 2023; Weinberg et al., 2015; Ruchsow et al., 2004, 2006; Schrijvers et al., 2008; Figure 1.9) amplitude relative to healthy controls, or no differences (Olvet et al., 2010; Riesel et al., 2019; Schoenberg, 2014). Overall, although the ECI model has been supported across multiple levels of analysis, the nature of emotional reactivity impairments in depression and their role in the development of the disorder is largely still unclear.

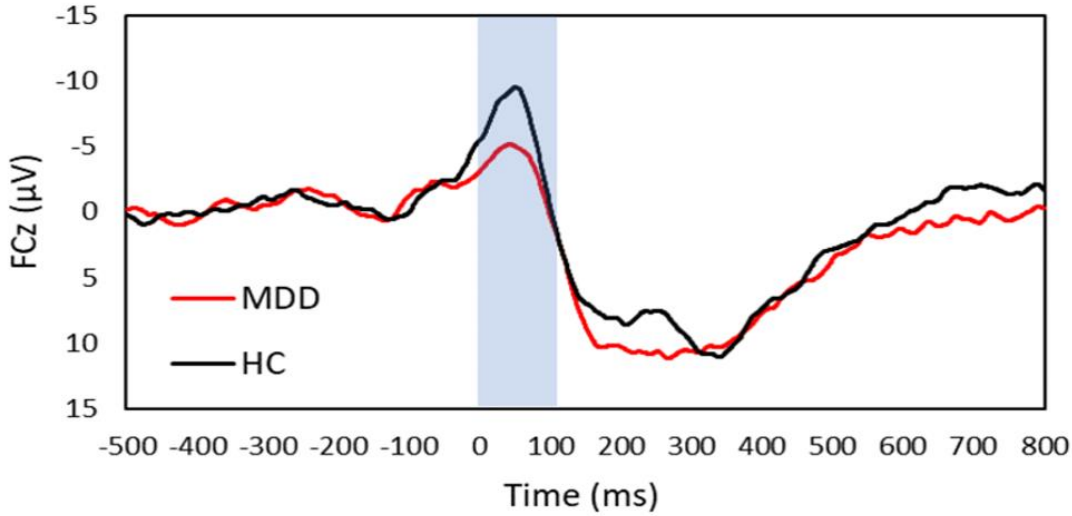

Figure 1.9 Response-locked event-related potential (ERP) waveforms for the difference between error and correct trials (ΔERN) in the MDD group (red line) and HC group (black line). The graph shows a reduced ERN in the MDD vs. the HC group. *From Dell'Acqua, Hajcak, et al., 2023.*

1.3 Cognitive Models

1.3.1 Classical Cognitive Model of Depression

The first cognitive model of depression was developed about 50 years ago and it postulates that one's thoughts, inferences, and interpretations can influence the onset and course of depression (Beck, 1987). Particularly, Beck's model holds that the self-referential schemas – internally stored representations of loss, worthlessness, and failure – lead individuals to filter environmental cues such that their attention is directed toward mood-congruent stimuli. Beck argued that these representations lead individuals to have a negative perception of themselves, the world, and the future – also known as the cognitive triad. Moreover, the negative schemas induce individuals to have negative information processing biases which, in turn, contribute to the severity of the disorder. According to this theory, individuals tend to interpret emotionally ambiguous information negatively, show difficulties in disengaging their attention from negative information, and usually report general and more negative memories rather than specific and positive ones. Adverse early life events are thought to contribute to the development of latent depressive self-referential schemas that can, later, be re-activated following a negative or stressful event (Disner et al., 2011; Figure 1.10).

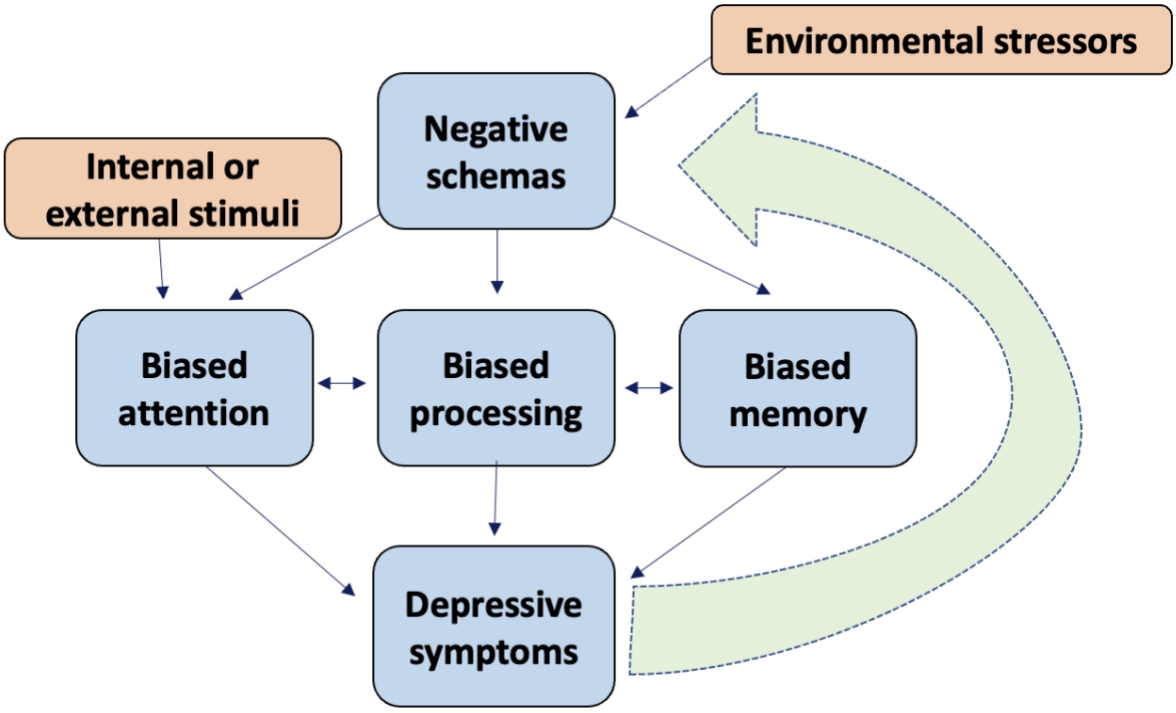

Figure 1.10 Illustration of the cognitive model of depression. Negative schemas - activated by environmental stressors – lead to biases in attention and memory that, in turn, contribute to depressive symptoms. Once the schema has led to depressive symptoms, the schema itself is strengthened. *Adapted from Disner et al., 2011.*

The activation of depressive schemas, hence, leads to biases in attention and memory. A meta-analysis comprising 29 empirical studies that employed different paradigms supported the existence of biased attention in depression (Peckham et al., 2010). Diverse computerized speeded reaction times paradigms have been developed to study the degree of impaired disengagement from unpleasant stimuli. For example, the emotional version of the Stroop task (Stroop, 1935), whereby participants are asked to indicate the print color of emotional (pleasant and unpleasant) and neutral words while ignoring the meaning of the words themselves, has been employed to study attention bias in depression (Figure 1.11). Usually, healthy controls, have greater latencies in naming colors of both unpleasant and pleasant words compared to neutral items. A greater bias for unpleasant mood-congruent stimuli was reported in individuals with clinical depression (Epp et al., 2012; Fritzsche et al., 2010), subclinical depression (Gantiva et al., 2018; Kaiser et al., 2015), in healthy individuals subjected to sad mood induction (Gilboa-Schechtman et al., 2000; Isaac et al., 2012; Provenzano et al., 2019), and

women with familiarity to depression (van Oostrom et al., 2013). However, other studies did not report this attentional bias in subclinical depressive symptoms using the emotional Stroop task (Dell'Acqua et al., 2021).

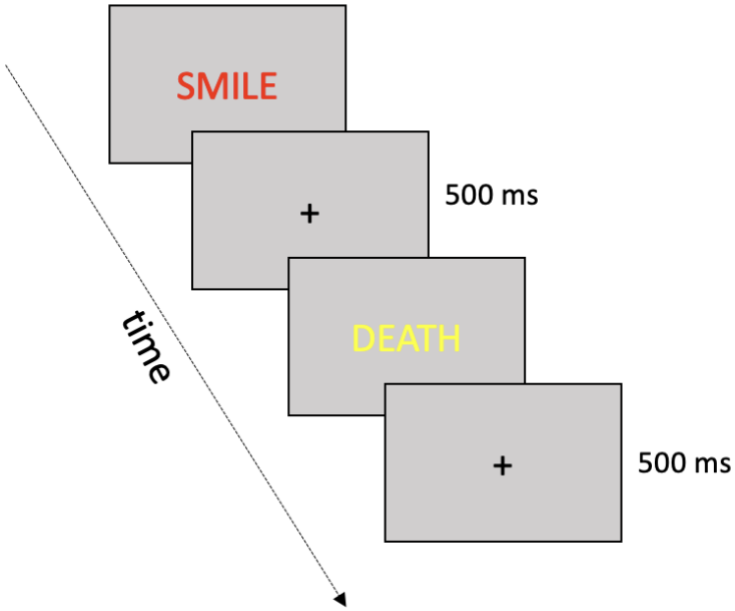

Figure 1.11 Illustration of the emotional Stroop task.

In addition to speeded tasks, eye-tracking studies demonstrated that individuals with depression tend to spend more time attending to unpleasant images than controls (Kellough et al., 2008). Another study showed that individuals with depression spent less time attending to pleasant images (Sears et al., 2010). Indeed, meta-analytic evidence on eye-tracking research supported greater attention to negative stimuli and less attention to positive stimuli in adult males (Armstrong & Olatunji, 2012). Notably, recent studies have reported attentional biases away from positive information (for a review see Winer & Salem, 2016), suggesting an attentional avoidance of pleasant and rewarding stimuli.

Memory biases consist in preferentially recalling negative events and overgeneralized autobiographical memories. The self-referential recall is typically assessed with the self-

referent encoding task (SRET) which requires participants to read a list of negative and positive adjectives and indicate whether each word describes them. Then, participants are unexpectedly asked to recall as many adjectives as possible. Children and adults with depression tend to recall more negative words than positive ones compared to controls (Connolly et al., 2016; Gotlib et al., 2004).

1.3.2 Executive Functions

Executive functions (EFs) - also called cognitive or executive control - include a set of top-down cognitive processes that influence lower-level processes and are involved in goal-directed behaviors (Friedman & Myake, 2017). These high-order processes are strictly tied to motivation and allow the active maintenance of goal representations and flexible achievement of goal-directed behavior. Executive functions are particularly important in novel circumstances, when task goals must be actively maintained, distracting information must be inhibited, or when habitual responses must be overcome (Baddeley, 1996; Burgess & Shallice, 1996). Specifically, these processes enable several skills, such as suppressing automatic responses, inhibiting interfering and irrelevant information, planning, monitoring, maintaining, updating, and manipulating information. Numerous models and definitions have been proposed and a common point across all of them is that they view EFs as a multidimensional construct, namely a set of separable units. A meta-analysis of more than 100 studies has identified 39 different processes used to describe the organization of executive functions (Baggetta & Alexander, 2016). The most investigated process is inhibition, defined as the ability to control or inhibit prepotent automatic responses. Then, another commonly studied process is working memory, defined as the ability to maintain, add new information, and remove unnecessary information. The third most investigated process is set-shifting, which is the ability to shift from one task to another (Baggetta & Alexander, 2016).

Executive functions are implemented in the prefrontal cortex (PFC) and several theoretical models have been based on the anatomical dissociation among distinct processes in this brain region. The ROtman-Baycrest Battery to Investigate Attention (ROBBIA) model was firstly proposed by Stuss in 1995 and is based on neuropsychological and neuroimaging studies. This model firstly hypothesized five processes related to different PFC subregions: energization, task-setting, monitoring, inhibition, and logic (Stuss et al., 1995). Over the years, the model has been revised and of the five originally suggested processes, only three have been supported: task-setting, monitoring, and energization. These processes are believed to be dissociable anatomically, with a left-right hemispheric specialization in the PFC (Vallesi, 2021). Task (or criterion) setting is thought to be related to left PFC functioning and is defined as a process responsible for creating and selecting associations or rules that are relevant for achieving a goal and actively suppressing the interfering irrelevant information (Ambrosini et al., 2019; Stuss & Alexander, 2007; Vallesi, 2012). Criterion setting is a phasic proactive process mainly activated when individuals need to learn a new task-rule or when the task requires dynamic changes of task rule, for example in a task-switching paradigm (Vallesi, 2021). Instead, monitoring mostly relies on the right PFC functioning and is defined as the cognitive control process responsible for actively maintaining representations of task-relevant information and making behavioral adjustments to optimize performance (Stuss & Alexander, 2007; Vallesi, 2012). Monitoring is sort of a reality check process that carefully assesses environmental and internal circumstances to make sure the goal is achieved. Energization is a complementary process boosting other operations that lose activation either because they are too complex or because of fatigue (Vallesi, 2021). This last process is associated with the activity of the superior medial prefrontal regions, such as the anterior cingulate cortex (Stuss et al., 2005; Stuss et al., 2002). In this revised version of the ROBBIA model, inhibition was not included as a dissociable process, as inhibitory control can be explained by the

simultaneous work of energization, task-setting, and monitoring (Stuss & Alexander, 2007; Friedman & Miyake, 2017). A way to assess criterion-setting and monitoring is to employ a task-switching paradigm with both single-task and mixed-task blocks (Figure 1.12). Single task-blocks require participants to perform a task in isolation, while mixed-task blocks are composed of intermixed rules (switch and repeat trials) (Meiran, 2010; Monsell, 2003). This paradigm evaluates the cost of switching from one rule to the other, the cost of keeping multiple task-sets active, and the disengagement from a previous task-set and stimulus (Meiran, 2010; Monsell, 2003). Specifically, criterion-setting can be assessed with the switching-cost, by calculating the performance difference between switch and repeat trials. Moreover, monitoring can be assessed with the mixing cost, by calculating the performance difference between repeat and single trials (Monsell, 2003; Rubin & Meiran, 2005). Overall, the ROBBIA model and the dissociation between these two processes have been strongly supported by multimodal cognitive and neuroscientific approaches (Vallesi, 2021). Yet, this model has been rarely applied to psychopathology and, especially, the study of cognitive control in depression.

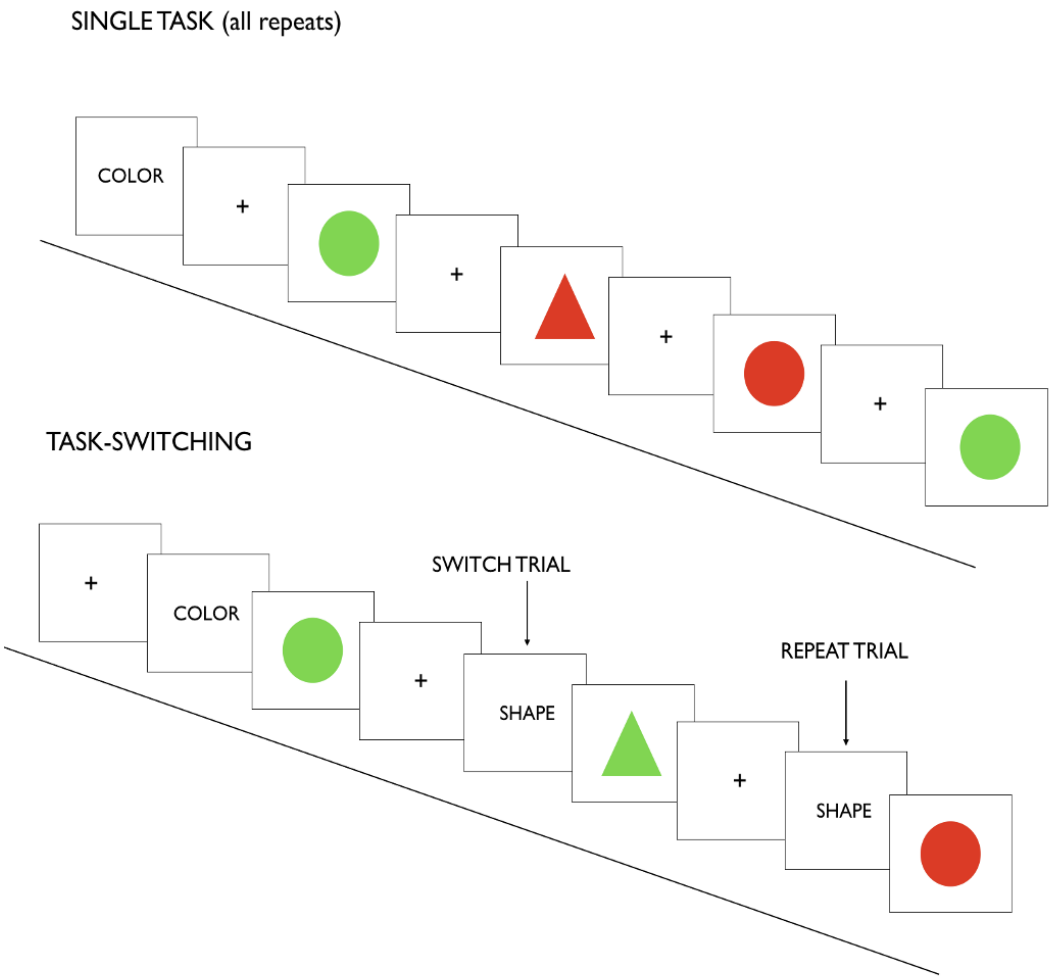

Figure 1.12 Illustration of a task-switching paradigm. Switching costs are calculated by subtracting response times (RTs) of switch trials from RTs of repeat trials. Mixing costs are calculated by subtracting RTs of repeat trials from RTs of single trials.

1.3.3 Executive Functions Impairments and the Role of Emotions in Depression

As mentioned above in Section 1.1, the DSM-5 included as a diagnostic criterion for depression the "inability to think or concentrate", suggesting that cognitive impairments constitute a core component of this disorder. This is not surprising since **cognitive control** is crucial in **motivated behavior** and, as described above, depression is related to deficits in motivation. However, despite models of depression highlighting the role of cognition and emotions, the association between these two aspects has rarely been examined systematically.

Consistently, a recent line of research has focused on exclusively studying general impairments in cognitive control in the absence of emotional material – also defined as *cold*

EFs. Studies in this field have reported reduced cognitive control across different tasks in individuals with depressive symptoms (e.g., Dotson et al., 2020; Harvey et al., 2004; Lin et al., 2014; Parkinson et al., 2020). For example, depression was related to difficulties in adjusting to single-task conditions after experiencing task-switching blocks, poor updating, and less task preparation (Hoffmann et al., 2017; Meiran et al., 2011). These impairments seem to be present even in remitted individuals (Rock et al., 2014). At the neural level, cognitive control deficits in depression have been related to reduced resting state or task-related activity in frontal regions, such as the dorsolateral prefrontal cortex and the anterior cingulate cortex (Gotlib & Hamilton, 2008; McTeague et al., 2017).

Another line of research suggests that individuals with depression are not characterized by global cognitive control difficulties, but rather by specific deficits in emotional, or *hot*, contexts. Based on early cognitive theories of depression (Beck, 1987), these studies have explored the preferential processing of unpleasant stimuli and the consequent difficulty in suppressing negative material across a variety of computerized tasks. However, most studies have only used one task (emotional) without comparing participants' performance with a non-emotional task version. Depression seems to be related to difficulties in switching away from or inhibiting unpleasant stimuli (e.g., Everaert et al., 2017; Epp et al., 2012; Wen & Yoon, 2019), and updating working memory when the content is negative (Levens & Gotlib, 2010), supporting the view that unpleasant content interferes with cognitive control functions (LeMoult & Gotlib, 2019). Findings are more mixed on cognitive control over pleasant content in depression, with studies documenting better (Deveney & Deldin, 2006) or poorer cognitive control over pleasant stimuli relative to controls (Quigley et al., 2020). Some of these studies have employed an emotional version of the task-switching paradigm, whereby target stimuli are emotionally valenced images (usually faces) instead of colored shapes. Moreover, a study that used a simple task-switching paradigm that provided performance feedback (Figure 1.13),

which in healthy individuals is known to improve speed and accuracy, showed that depressive symptoms were not related to the feedback effect (i.e., reward-learning, Ravizza & Delgado, 2014). In other words, the deficits in processing the affective component of feedback influenced cognitive control abilities in individuals with greater depressive symptoms. Taken together, it remains to be elucidated whether shifting difficulties in depression occur globally or are specific to the emotional context.

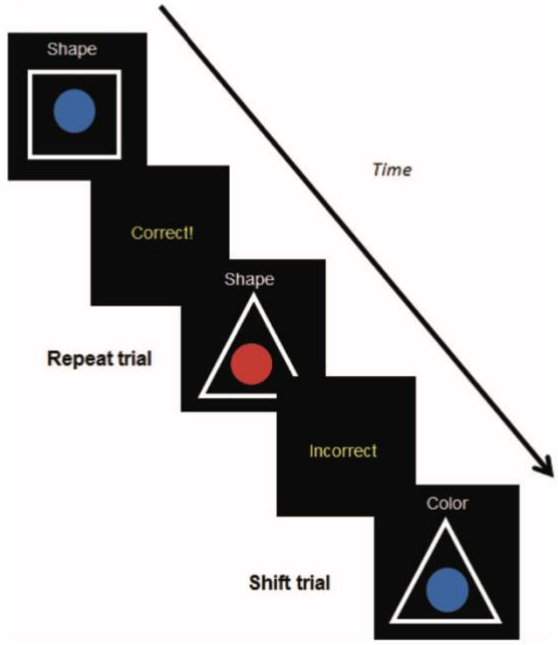

Figure 1.13 Illustration of the task-switching paradigm where performance feedback is provided at every trial. *From Ravizza & Delgado, 2014.*

Despite the evidence supporting reduced cognitive control in depression, current knowledge on cognitive control in depression is mainly descriptive and research views cognitive control deficits in depression as reduced ability to exert control but does not provide a specific model. Particularly, there is a lack of integration between cognitive and motivation-affective impairments in depression. Whether depression is related to a general difficulty in exerting cognitive control or to a selective difficulty in exerting cognitive control over emotional content is mainly unexplored. Although cognitive control in *cold* contexts does not directly involve emotional processing, it has been suggested that it may facilitate performance in hot contexts, counteracting the risk conferred by depression-related emotion-processing

biases (Roiser et al., 2012; Roiser & Sahakian, 2013). Therefore, depressive symptoms may be associated with general cognitive control difficulties that, in turn, affect control over emotional information. Instead, based on the classical cognitive perspective, negative schemas may generate a processing advantage for unpleasant stimuli, leading to an altered encoding and processing of every other information (Beck & Bredemeier, 2016). Therefore, individuals with depressive symptoms may display cognitive control difficulties in *hot* contexts not because of impaired general mechanisms, but because of enhanced orienting and attention to unpleasant stimuli that impact cognitive control functions (Lo & Allen, 2011).

CHAPTER II

ELECTROENCEPHALOGRAPHIC (EEG) CORRELATES OF AFFECTIVE AND COGNITIVE PROCESSING

Over the past decades, electroencephalography (EEG) proved to be a valuable tool in both clinical and scientific applications. The EEG has been particularly useful in the study of emotional processing and has been widely used in the field of affective neuroscience (e.g., Keil, 2013). However, the raw EEG signal is a conglomeration of many distinctive neural sources of activity that need to be extracted to isolate specific cognitive processes (Luck, 2014a). To do so, there are different techniques, some are simple (event-related potentials), and others are more advanced and sophisticated (time-frequency analyses). Research on EEG event-related brain activity began in the 1930s and was mainly focused on sensory processes, it then shifted to the study of top-down processes answering questions of broad scientific interest (Luck, 2014a).

In the present Chapter, following an introduction to the EEG signal and its basic principles, event-related methods and the emotional modulation of EEG frequency bands and its relevance for the study of depression will be described.

2.1 The EEG Signal: Basic Principles

The EEG is a bioelectric potential recorded from the surface of the head using specific electrodes. The human EEG was firstly registered by Hans Berger in 1929 and, in a little more than 10 years, all frequency bands had been observed and categorized. An in-depth description of EEG and its principles is beyond the scope of this work, and complete reviews can be found elsewhere (e.g., Luck & Kappanman, 2011; Luck, 2014a). In brief, there is a consensus that the major sources of the EEG signal are superficial giant pyramidal neurons in the upper layers of the cerebral cortex (Buzsáki et al., 2012). The electroencephalographic signal mainly reflects

the summation of excitatory (EPSP) and inhibitory (IPSP) postsynaptic potentials at the dendrites of groups of neurons with parallel geometric orientations (Figure 2.1). As neurotransmitters activate ion channels on the cell membrane, ions flow into and out of the neuron from and to the extracellular space, producing electrical fields that surround the neuron. In the case of ESP, when the neurotransmitters are released, a positive ions flux (NA^+ or Ca^{2+}) flows from the extracellular into the intracellular space, resulting in a negative local field potential. At the same time, to maintain electro-neutrality, an opposing current moves from the intracellular to the extracellular space along the neuron, resulting in a positive local field potential. By generating these current flows, neurons act as electrical dipoles (Buzsáki et al., 2012).

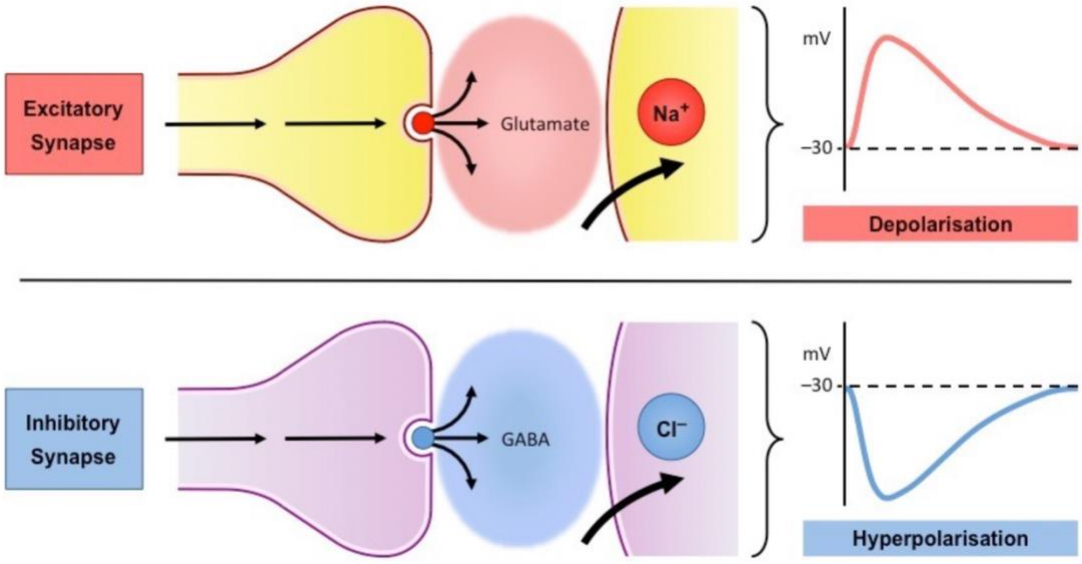

Figure 2.1 Neurotransmitters released by the presynaptic neuron diffuse into the synapse and bind receptors on postsynaptic neurons. Some neurotransmitters (e.g., glutamate, top) generate excitatory post-synaptic potentials (EPSPs) and trigger depolarization; while others (e.g., GABA, down), generate inhibitory post-synaptic potentials (IPSPs) and trigger hyperpolarization. *From Bioninja.com (link to page: https://rb.gy/0gbpus*).

The electrical field generated by one neuron is too weak to be measured from one EEG scalp electrode, but as the neural activity gets synchronous across thousands of neurons, the electrical fields generated by individual neurons sum, and the resulting field becomes powerful enough to be measured from the scalp (Cohen, 2014; Murakami & Okada, 2006). However, if

the cells are not aligned in a parallel fashion, as in the case of the subcortical regions, then the recorded potential is very small, due to cancellation.

The EEG signal is oscillatory in nature. Brain oscillations are rhythmic fluctuations in the excitability of groups of neurons and are linked to many neurobiological events (e.g., cognition, emotions, consciousness; Figure 2.2). EEG oscillations are characterized by a specific morphology, frequency, and amplitude. The frequency of the oscillations represents the speed of the signal in terms of cycles per second and is measured in hertz (Hz). The amplitude represents the size, or height of the wave and is measured in microvolts (μV). Frequency and amplitude are not independent parameters, but with the increase of one, the other decreases. Since Berger's studies, brain oscillations were classified into distinct frequency bands based on the visual inspection of the raw signal. The main frequency bands are delta (δ, frequency 0.5–4 Hz; amplitude > 100-200 μV), theta (θ, frequency 4-8 Hz; amplitude 50-200 μV), alpha (α, frequency 8–13 Hz; amplitude 30-50 μV), beta (β, frequency 13–30 Hz; amplitude <20 μV) and gamma (γ, frequency > 30 Hz; amplitude <5 μV) (International Federation of Societies for Electroencephalography and Clinical Neurophysiology, 1974).

Typically, EEG oscillations reflect the level of arousal and activation induced by an event or in resting conditions (Berger, 1969). For instance, slow frequencies in the delta and theta range, are prevalent during deep sleep, while alpha waves are associated with a state of idleness, and faster rhythms are related to active wakefulness (e.g., Kilner et al., 2005). Delta, theta, and alpha bands are distributed across large cortical regions and are the product of the synchronous activity of large groups of neurons (Knyazev, 2007). Consistently, these frequencies are considered *global processing modes* and seem to reflect the integrations and synchronization across distant and spatially distributed regions (Nunez, 1995; Knyazev, 2007). Contrariwise, beta and gamma bands are considered *local modes* and are distributed over more

limited regions. In conditions of rest and stimulation, each frequency band has been linked to specific processes, such as perception, categorization, emotions, and actions (Knyazev, 2007). The functional role of the main frequency bands in emotional processing will be discussed later in this Chapter.

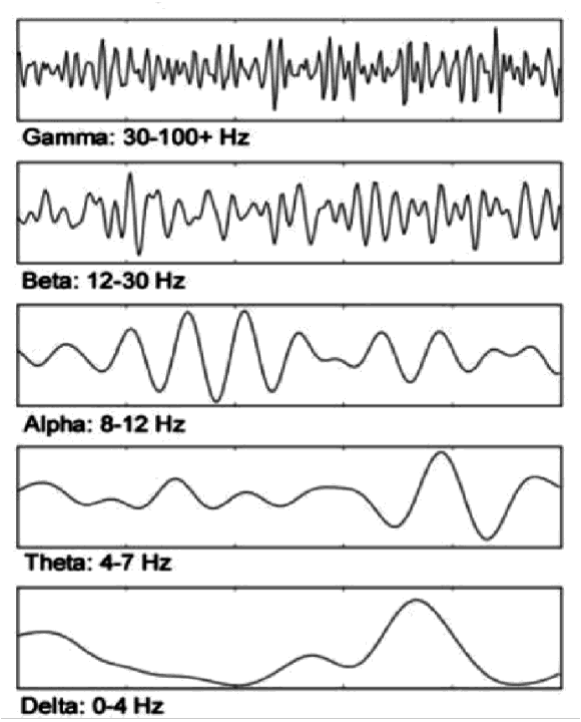

Figure 2.2 Major EEG frequency bands. *From Nacy et al., 2016.*

The EEG signal contains a combination of simultaneous oscillations at different frequencies and amplitudes, but it is possible to separate the features of each individual wave (Figure 2.3). To achieve this, a common methodological tool is the Fast Fourier Transform (FFT), a mathematical procedure that computes the amplitude, frequency, and phases of the sine waves that compose a given EEG signal (Luck, 2014a). The FFT extracts the power spectrum by decomposing the sine waves that constitute the signal and computes the power (frequency expressed in amplitude^2) for each frequency band (Buzsáki, 2006). In task-related designs, the continuous EEG signal is divided into shorter segments to compute the FFT, as this method assumes the stationarity of the signal (i.e., the same mean and variance) and does take into account the time course of the signal (Cohen, 2014).

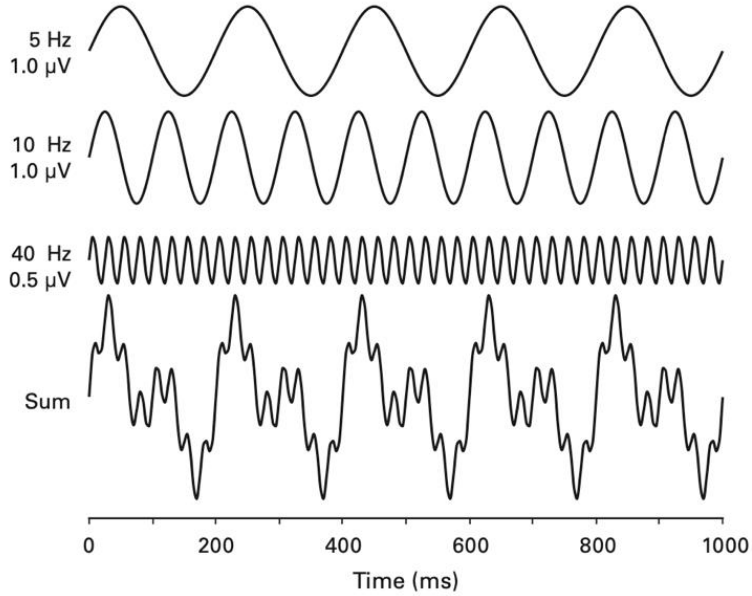

Figure 2.3. Example of the summation of oscillations at different frequencies. The figure illustrates three different kinds of sine waves and their summation below. The FFT determines the amplitude, phase, and frequency of the waves that sum together to form the continuous EEG. *From Luck, 2014a.*

2.2 Event-Related Potentials (ERPs): A Consolidated Approach to the Study of Emotional Processing

Event-related potentials (ERPs) are powerful tools for measuring the dynamics of human neural activity and they have been widely used to investigate numerous cognitive functions. Particularly, ERPs reflect the temporary changes in the EEG signal induced by external stimulation. The EEG signal is often recorded during paradigms where events are repeated across multiple trials, which are then averaged to isolate the activity related to the event, namely the event-related potential (Luck, 2014a). The averaging is needed to cancel out the noise that is contained in every trial, thus isolating the signal of interest related to the external stimulus (the ERP, see Figure 2.4). The result is a series of negative and positive deflections that vary in amplitude and duration within a certain time window (Keil, 2013). Specifically, ERP waveforms can be defined as "*a depiction of the changes in scalp-recorded voltage over time that reflects the sensory, cognitive, affective, and motor processes elicited by a stimulus*" (Luck & Kappenman, 2011). The amplitude of the peak reflects an index of the

strength of the underlying process, while the latency regards the timing and duration of the response. The naming of ERP components reflects their polarity (P for positive or N for negative) and latency (when the component usually appears following stimulus onset). Some components' names are not based on the latency but on the ordinal position of the peak in the waveform (e.g., N1 for the first negative peak; Luck, 2014a). Some ERP components are labeled with functionally descriptive names (i.e., late positive potential or LPP).

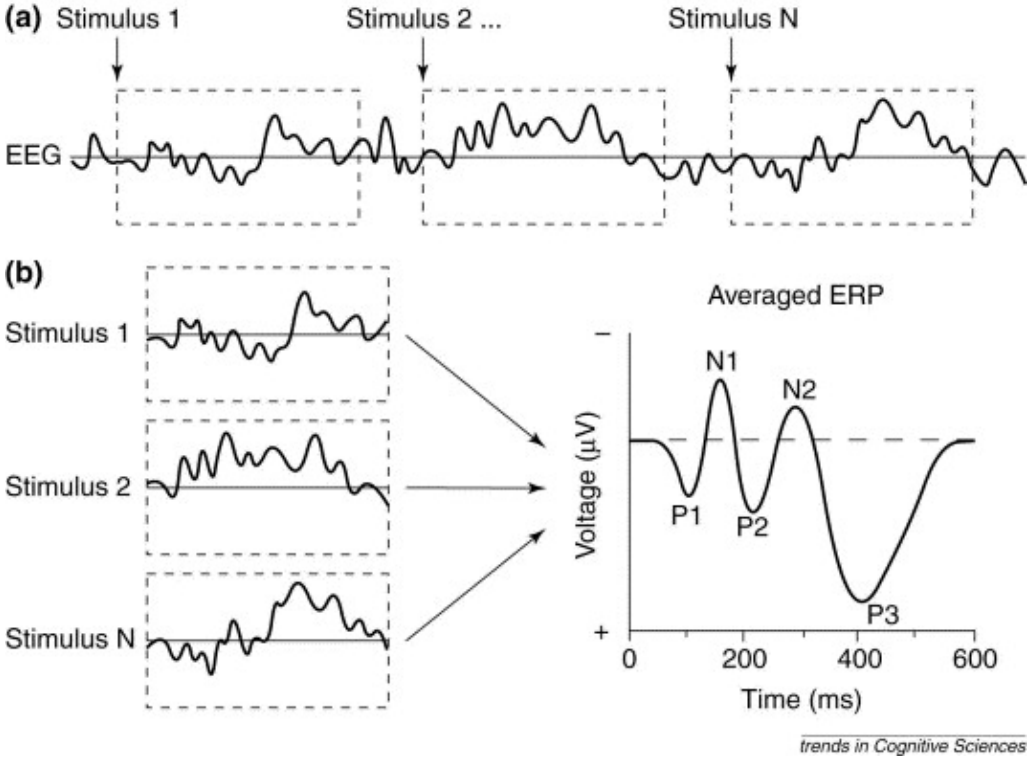

Figure 2.4. Computation of the ERP waveform from continuous EEG data. (a) Stimuli are presented during the EEG recording, but the exact response to each stimulus is not large enough to be observable. (b) To isolate event-related activity from the continuous EEG, segments around each stimulus are extracted and averaged together to compute the averaged ERP waveform. *From Luck et al., 2000.*

ERPs provide a direct, millisecond-resolution measure of neural activity. This is in divergence with the blood oxygen level-dependent (BOLD) signal assessed with the functional magnetic resonance imaging (fMRI), which is delayed by several seconds. Thanks to the elevated temporal resolution, ERPs have been used in many studies to explore and outline the time course of emotional reactivity in healthy individuals (e.g., Olofsson et al., 2008; Codispoti et al., 2007). A review of more than 50 studies that have used ERPs to study emotional processing and reactivity in healthy adults revealed that the components implicated in

emotional reactivity begin around 200-300 ms post-stimulus and can vary in amplitude based on arousal and, sometimes, valence (Olofsson et al., 2008). Within the first 300 ms post-stimulus onset, ERPs reflect the early perceptual encoding of the stimulus (Olofsson et al., 2008). For example, for visual stimuli, the P1 (occurring about 80-130 ms after stimulus onset) and the successive N1 (occurring about 100-150 ms after stimulus onset) peaks mirror the early processing of perceptual elements of the stimulus within the visual cortex. Studies examining these early components reveal mixed findings regarding their potential affective modulation. However, some evidence supports that highly arousing unpleasant images produce larger N1 amplitudes relative to pleasant and neutral stimuli, supporting the hypothesis of a fast neural threat-detection mechanism (Olofsson & Polich, 2007; Smith et al., 2003; Williams et al., 2006).

Components occurring later (e.g., those evident after 300 ms stimulus onset) reflect more elaborated processing of stimulus content, resource allocation, saliency detection, cognitive effort, and memory processes (Luck, 2005; Olofsson et al., 2008). The amplitude of the P3 component is larger to infrequent than frequent stimuli in oddball paradigms, indicating its link to stimulus novelty. The Late Positive Potential (LPP), a positive component that begins around 300 ms after stimulus onset, has been found to be particularly important for the study of emotional reactivity to affective information. The LPP appears to mirror motivated attention following the activation of the motivational systems (approach and avoidance, see Chapter I). However, the LPP reflects the current motivational state but not its specific direction (appetitive or defensive). The LPP is often investigated through affective picture viewing paradigms in which pleasant, neutral, and unpleasant pictures are presented over periods of several seconds. These studies reveal that the magnitude of the LPP over the centroparietal cortex consistently increases in amplitude as arousal levels increase for both unpleasant and pleasant relative to neutral images (e.g., Cuthbert et al., 2000; Codispoti et al., 2007;

Dell'Acqua, Moretta, et al., 2022; Schupp, et al., 2004; Palomba et al., 1997; Figure 2.5). This sustained positivity for highly arousing images is evident across the duration of the picture presentation (Hajcak & Foti, 2020). The first portion of the LPP (300-600 ms) partly overlaps with the P3, while following 600 ms the LPP mostly mirrors stimulus content and meaning and not to perceptual processing (De Cesarei & Codispoti, 2006). Indeed, emotion modulation of the LPP is a robust phenomenon and it has been shown to be independent of stimulus size (De Cesarei & Codispoti, 2006), or duration (Codispoti et al., 2007). This component has been thoroughly explored and research showed that it has elevated temporal stability over weeks (Codispoti et al., 2007). Interestingly, early ERPs components reflecting perceptual processing were not correlated with the LPP and were not stable over time, indicating that the LPP is uniquely linked to emotional responding (Codispoti et al., 2007).

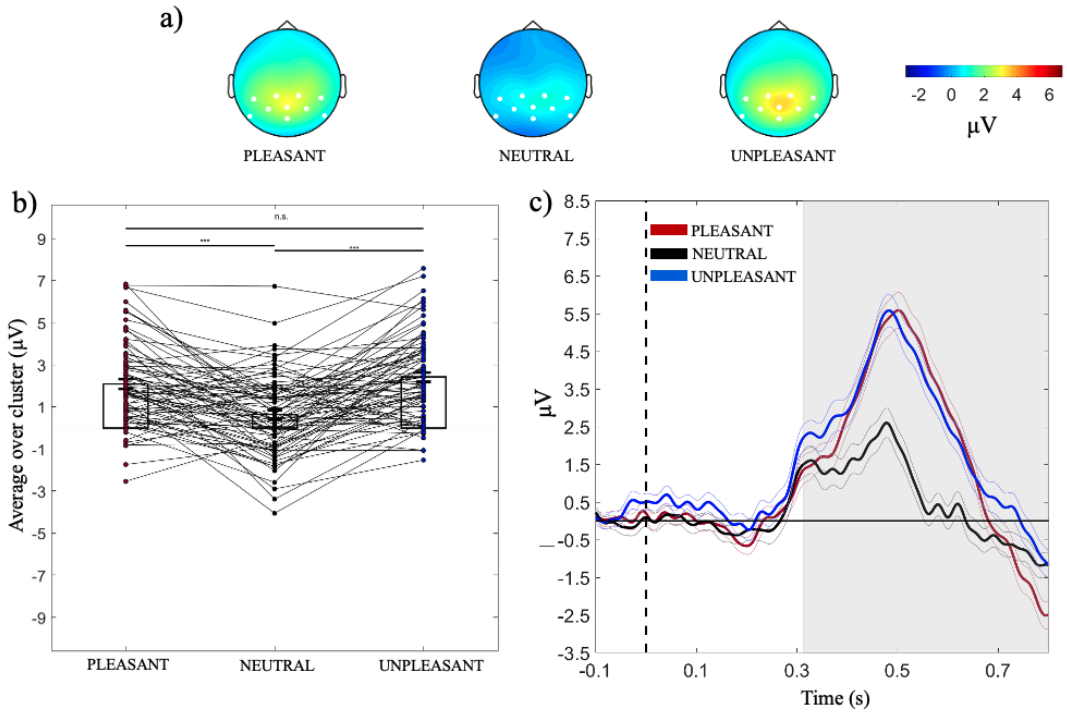

Figure 2.5 Illustration of the LPP in response to pleasant, neutral, and unpleasant images. (Panel a) Topography of the mean LPP amplitude (μV) averaged over the time window 312–800 ms for pleasant, neutral, and unpleasant conditions. (Panel b) Mean amplitude of the LPP of each participant averaged over the significant electrodes and time points for pleasant, neutral, and unpleasant conditions. Each circle represents one participant; black frames represent the mean ERP amplitude across all participants and the solid black lines represent ± standard error of the mean (SEM). ***p < .001. (Panel c) Time course of grand-average LPP waveforms averaged over the significant electrodes for pleasant (red line), neutral (black line), and unpleasant (blue line) conditions. *From Dell'Acqua, Moretta, et al., 2022.*

ERPs for the study of emotional processing in depression

Most studies using ERPs in depression have examined the N2 and P3 components during the oddball paradigm, a non-emotional task in which participants are required to respond to an infrequent sound. Individuals with depression showed reduced N2 and P3 amplitudes, indicating difficulties in automatic attention and stimulus processing (Bruder et al., 2012; Hajcak Proudfit et al., 2015). Moreover, individuals with anhedonia and dysthymia showed reduced P3 amplitudes to memory tasks compared to controls and failed to appropriately respond to varying task demands, indicating that these individuals have difficulties in resource allocation strategies (Yee & Miller, 1994).

Recently, ERPs research on depression has shifted its focus to the study of attention and processing of emotional stimuli (Hajcak Proudfit et al., 2015). Some studies on the processing of emotional words or faces found reduced N2 amplitude to positive cues in depression compared to neutral ones and controls (Deldin et al., 2000). Moreover, a larger P3 amplitude to negative words relative to neutral and healthy controls was reported in depression, supporting the view of increased orienting and processing of negatively valenced stimuli in depression (Ilardi et al., 2007). These results indicate that depression might be related to early attentional and orientation difficulties toward affective stimuli (i.e., reduced early processing of pleasant and increased processing of unpleasant stimuli).

Given its robust role in discriminating emotional vs. neutral cues, the LPP has been the object of thorough investigation in depression in the last decade. Although cognitive models suggest that depression is related to increased processing of unpleasant content, not many studies have found greater LPP amplitudes for unpleasant stimuli in depression (Benau et al., 2019). On the contrary, a series of studies have reported a blunted LPP to negative (threatening) but not neutral content in depression (Foti et al., 2010; MacNamara et al., 2016; Weinberg et al., 2017) and in individuals at risk for depression (Kujawa et al., 2012) relative to controls.

Moreover, blunted LPP when viewing pleasant stimuli has been found in depression (Grunewald et al., 2019; Weinberg et al., 2016; for a review see Hajcak Proudfit et al., 2015), in children with depressive symptoms (Kujawa et al., 2011; Whalen et al., 2020) or at risk for depression (Levinson et al., 2018; Nelson et al., 2015), and to prospectively predict depression onset (Sandre et al., 2019). Taken together, these studies suggest that depression and depression risk might be characterized by reduced attention toward positively valenced content instead of an automatic orientation toward negatively valenced content.

2.2.1. Advantages and Limitations of ERPs

The analysis of ERPs offers several advantages and is well-suited to the study of emotional processing. For instance, ERPs are simple and quick to compute and generally involve little data processing. Moreover, contrary to other more recently developed methods, the extensive literature on ERPs allows for contextualizing and interpreting new findings (Cohen, 2014). Also, many studies have investigated the psychometric proprieties of ERPs and found them to be extremely reliable in terms of internal consistency and test-retest variability (e.g., Ethridge & Weinberg, 2018; Weinberg & Hajcak, 2011).

However, ERPs do not come without limitations. First, some task-related trial-based information can be lost during ERPs averaging as it does not capture non-phase locked dynamics (i.e., that vary in latency, see Section 2.2.3 for more details). Second, ERPs are usually scored at one or a small pool of scalp sensors in a specific time window, which reduces the multidimensionality of the EEG signal down to two dimensions and does not allow investigating processes that occur simultaneously (Cohen, 2014). Finally, ERPs do not generally allow the analysis of whole brain activity, and many hypotheses cannot be tested with this method (Cohen, 2014).

2.3 A Shift Toward the Time-Frequency Approach

Although ERPs are considered a reliable and fruitful tool to examine task-related brain activity, other techniques, such as time-frequency analyses, that can extrapolate more information from the EEG time series have been developed (Cohen, 2014). As mentioned above, the EEG data contains rhythmic oscillations with different frequencies, features, and functional correlates. Indeed, changes in brain rhythmic activity reflect task demands and different perceptual, cognitive, motor, emotional, mnemonic, and other functional processes.

As previously mentioned, the Fast Fourier Transform assumes that the data is stationary within an epoch, which means that the statistics (i.e., mean, standard deviation) do not change over time within a given time window. However, this is not the case for task-related EEG data that is highly non-stationary, as task events trigger a cascade of processes that differ in latency and frequency (Cohen, 2014). Hence, to describe task-related characteristics, other methods that allow the examination of the oscillations' temporal dynamics, such as wavelet convolution applied within the time-frequency approach, can be applied (Cohen, 2014). With the time-frequency approach, the EEG time series is decomposed so that it localizes oscillatory activity in the temporal and spectral domains simultaneously (Herrmann et al., 2014).

The most diffused time-frequency method is perhaps the **complex Morlet wavelet transform** (Figure 2.6), although other methods exist (e.g., Hilbert transform). Morlet wavelets look like sine waves in the middle and are tapered off to zero at both ends and are the product of a Gaussian curve with a specific frequency (Cohen, 2014). Wavelets are used to localize changes in the frequency features over time. The key computation behind time-frequency analysis is convolution, which involves the multiplication (or dot-product) of two signals to produce a new signal that captures the common features between them (Cohen, 2014; Morales et al., 2022).

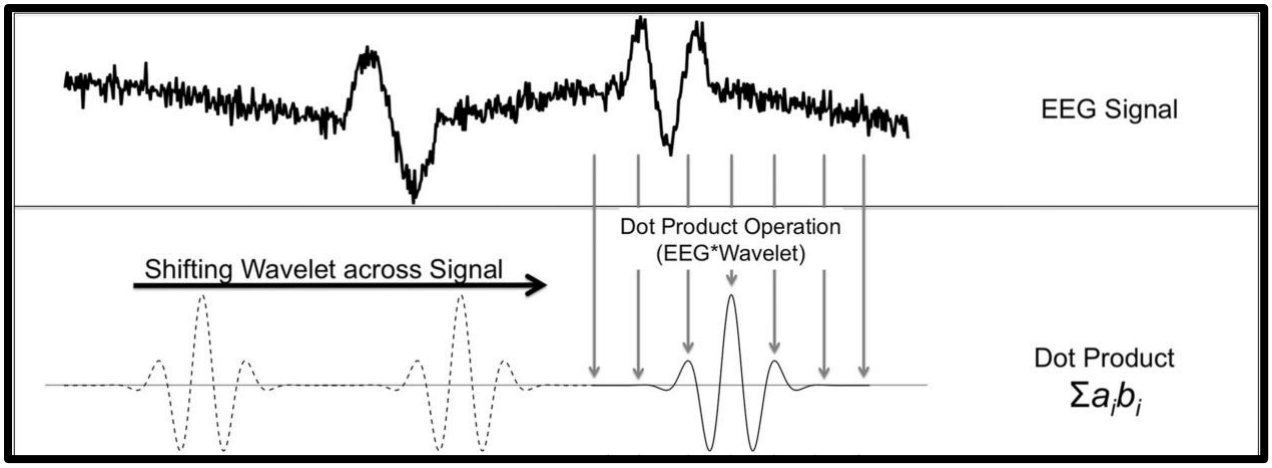

Figure 2.6 Illustration of Morlet wavelet convolution. The EEG time series (above) is convolved with a Morlet wavelet and this process is repeated along the signal by shifting the wavelet, yielding a time series that contains multidimensional information on the amplitude of the oscillations at each time point. *Adapted from Morales et al., 2022.*

In other words, the convolution of the wavelets with the event-related EEG signal in the time domain allows extrapolating power changes over time (Figure 2.7). The width of the central Gaussian (or full-width at half-maximum, FWHM) is a specific parameter that is set when computing Morlet convolution. There is a trade-off between temporal and frequency precision: the wider the central Gaussian, the less temporal precision but more spectral precision, and vice-versa for a thinner Gaussian (Figure 2.7; Cohen, 2019; Herrmann et al., 2014).

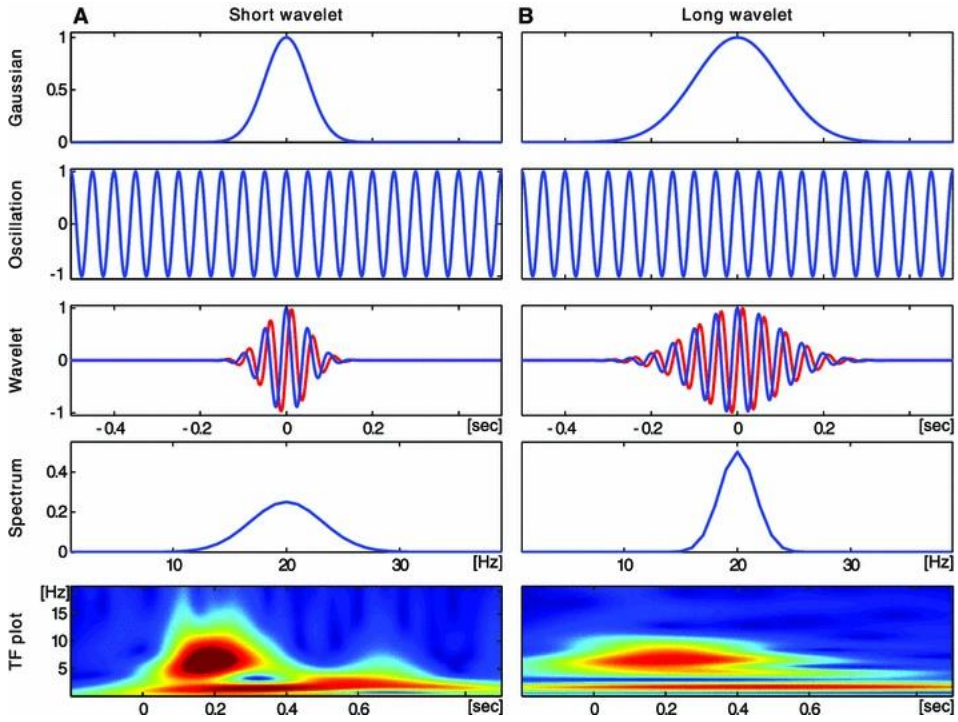

Figure 2.7 Illustration of the trade-off between temporal and spectral resolution of the wavelet transform. (Left) multiplying a *narrow* Gaussian with continuous oscillations leads to a wavelet with a shorter duration and wider spectrum. This will result in a time-frequency plot with high temporal resolution but less spectral precision (in the bottom figure, the responses above and below 5 Hz overlap). (Right) multiplying a *wider* Gaussian with continuous oscillations leads to a wavelet with a longer duration and smaller spectrum. This will result in a time-frequency plot with low temporal resolution but high spectral precision. *From Herrmann et al., 2014.*

The presentation of a stimulus or the activity related to a task elicits two types of event-related oscillations, namely evoked and induced activity. Evoked oscillations refer to brain responses occurring at the same latency in every trial. These oscillations are both time- and phase-locked to the stimulus. When averaging multiple trials to obtain event-related activity, evoked activity is entirely captured. Induced oscillations are time-locked to the stimulus but not phase-locked, namely, they occur within the same timing, but their peaks are not lined up. Therefore, in the ERP averaging the induced activity is lost (Figure 2.8). Results of a time-frequency analysis usually consist of the proportion of change in power following the event compared to a baseline and include both induced and evoked activity, namely total activity, or *event-related spectral perturbations* (ERSP; Herrmann et al., 2014). The results of time-frequency analyses often refer to *synchronization* (greater power) and *desynchronization* (reduction or suppression of power) of a frequency band.

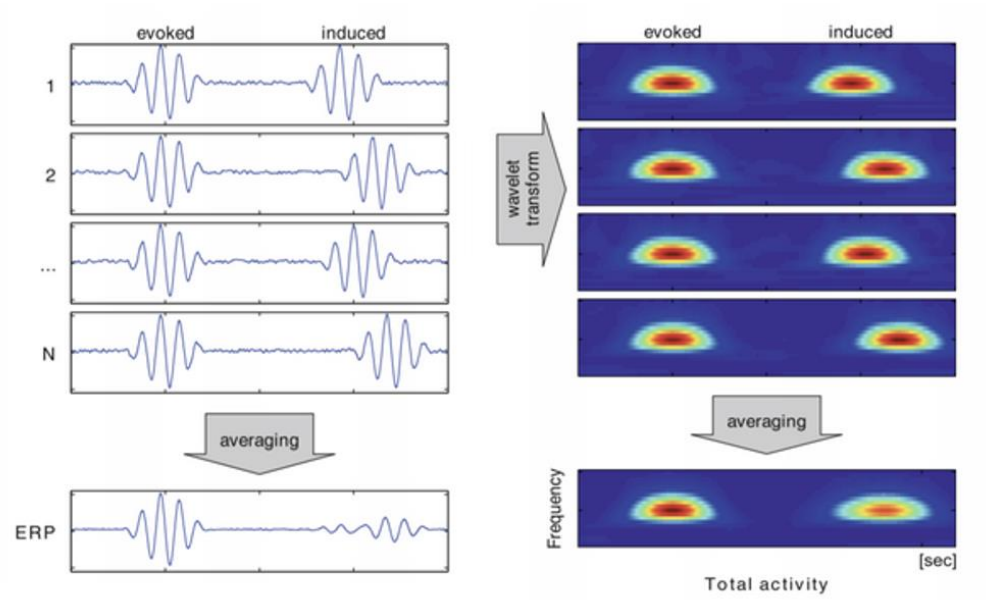

Figure 2.8 Left: illustration of evoked and induced activity. The evoked activity is characterized by a fixed temporal relationship between the phase position and the event so that a corresponding activity is also observed in the averaged signal. The induced activity also overlaps in time, but here the phase position varies from measurement to measurement so that the signal activity present in each trial is averaged out. Right: illustration of both evoked and induced oscillations obtained through time-frequency analysis at the single trial level. *From Herrmann et al., 2014.*

2.3.1 The Role of Event-Related Oscillations in Studying the Interplay Between Emotional and Cognitive Processing

The investigation of affective processing through time-frequency analysis has, among others, the advantage of being able to disentangle the brain's parallel processing of information. Indeed, each frequency band has a specific and distinct functional role. Studies on the processing of emotional material usually employ paradigms that involve the passive viewing of emotional pictures, video clips, or emotional sounds. These stimuli oftentimes are drawn from large and validated databases such as the International Affective Pictures System (Lang et al., 2008; see Chapter I). Each item in these databases has specific arousal and valence ratings, making it possible to study neural correlates of emotions in a dimensional fashion. Most studies have been conducted on healthy individuals and relatively little literature on time-frequency studies is present in depression or in individuals at-risk for depression. However, considering that different EEG bands reflect distinct phases and states of the processing of

emotional material, the application of this method to study emotional reactivity in depression is rather promising.

Delta oscillations are prevalent during sleep and inactive states. However, from simple oddball paradigms, it first appeared that **delta and theta** oscillations are predominantly contributing to the P300 (Başar et al., 2001; Karakaş et al., 2000; Yordanova et al., 2000). Hence, these oscillations show greater synchronization in response to target stimuli compared with non-target and simple sensory stimuli. Delta oscillations are also considered a measure of basic motivational drive, signaling basic needs such as food, sex, and sleep (Knyazev, 2012). This view originates from an evolutionary perspective, as these oscillations dominate lower vertebrates such as reptilians and fish during active behavioral states (Knyazev, 2012). The behavior of lower vertebrates is mainly oriented towards the acquisition of biologically salient resources to survive (e.g., food, mating), and these behaviors are generally guided by the activation of the reward systems of the brain. This is in line with most recent findings that showed that the main hubs of motivational appetitive/reward circuits (i.e., ventral tegmental area, nucleus accumbens, ventral striatum, and the medial prefrontal cortex), are responsible for generating delta oscillations (Knyazev, 2012; Figure 2.9). In addition, delta oscillations are implicated in the synchronization of brain activity with autonomic functions, and this offers further support to the role of the delta band in basic homeostatic needs. For example, HRV, as already mentioned an index of cardiac vagal control, was found to change parallelly with resting state delta EEG activity in humans (Jurysta et al., 2005; Yang et al., 2002).

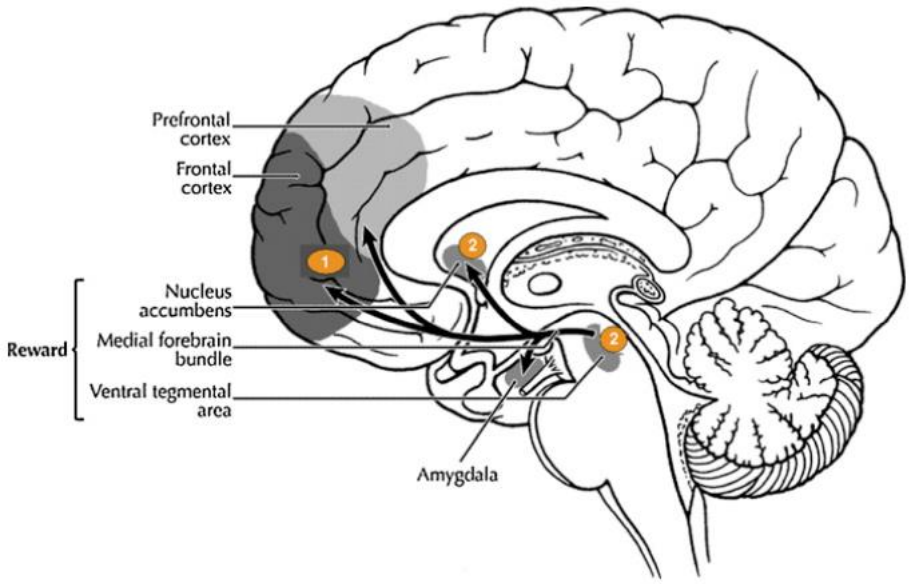

Figure 2.9 Localization of potential brain regions involved in the generation of delta oscillations as suggested by EEG source reconstruction, correlation of EEG data with imaging (i.e., fMRI and PET), and animal studies. *From Knyazev, 2012.*

Delta oscillations are believed to be sensitive to the motivational significance of the presented stimulus (Başar-Eroglu et al., 1992) and to play an important role in emotion processing (Knyazev, 2012). During paradigms that involve the passive viewing of emotional material, event-related delta power was reported to increase in response to highly arousing emotional (both pleasant and unpleasant) relative to neutral stimuli in healthy individuals mostly in centro-parietal regions (Aftanas et al., 2004; Balconi et al., 2009; Güntekin & Başar, 2016; Güntekin et al., 2017; Klados et al., 2009; Knyazev et al., 2009; Zhang et al., 2013). Indeed, in healthy participants, regardless of the valence of the image, intermediate and highly arousing images elicited greater delta power compared to low arousing ones (Aftanas et al., 2002; Klados et al., 2009; Figure 2.10). Moreover, Başar and colleagues showed that posterior delta power synchronization increased when viewing pictures of participants' grandmothers (Başar et al., 2007) and of loved ones relative to anonymous faces (Başar et al., 2008). Another research showed that neglectful mothers had reduced delta power in response to the presentation of non-infant affective pictures, suggesting they present limited emotional reactivity compared to non-neglectful mothers (León et al., 2014). Furthermore, a series of

studies has shown that delta synchronization relates to the processing of reward relative to loss cues, providing further evidence of the relation between delta oscillations and the sensitivity to reward and approach motivation (Cavanagh, 2015; Foti et al., 2015; Gable et al., 2021; Glazer et al., 2018). Additionally, a recent study reported that delta activity during a reward task was dampened by the intake of an opioid drug (buprenorphine), showing how opioidergic drugs can also modulate the engagement and task relevance (Peciña et al., 2019; Pfabigan et al., 2021).

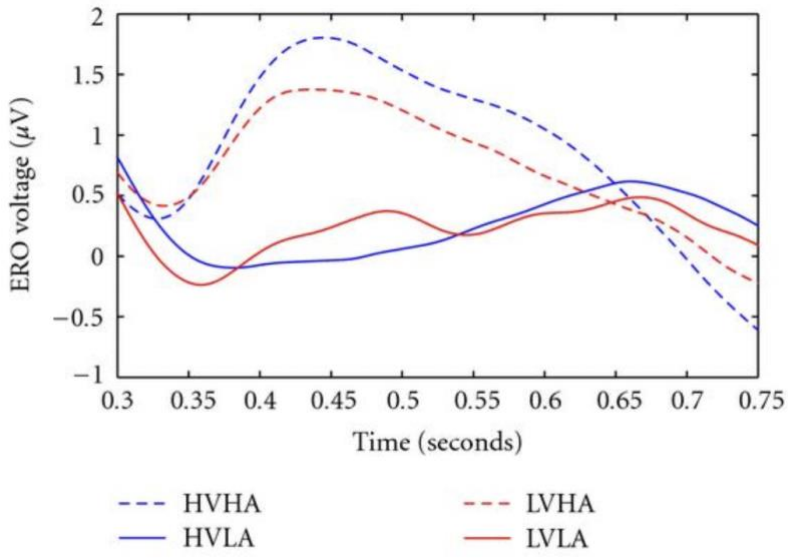

Figure 2.10 Event-related delta power to IAPS images with different arousal levels (low, high) and valence (high: pleasant, low: unpleasant). Delta power was greater in response to highly arousing pictures (high valence and high arousal, HVHA and low valence and high arousal, LVHA) regardless of their valence. *From Klados et al., 2009.*

To date, delta oscillations during affective picture-viewing tasks have not been explored in depression. A few studies have, however, compared delta power during the receipt of a reward relative to a loss in depression. These studies have reported a reduced reward-related delta in depression (Jin et al., 2019) and in healthy individuals before the onset of depressive symptoms (Nelson et al., 2018; Webb et al., 2021). These initial studies suggest that depression and its risk might be related to reduced sensitivity to rewards and, more in general, reduced approach motivation.

Similarly, to delta oscillations, resting-state **theta band** oscillations (4-8 Hz) are also prevalent during states of drowsiness and are inversely related to brain activation and arousal (Kilner et al., 2005). However, task-related theta power reflects cognitive effort and is thought to have specific significance for emotional processing (e.g., Başar-Eroglu et al., 1992). Indeed, theta oscillations are implicated in emotional processing and, like delta oscillations, have been reported to be increased for emotional relative to neutral content (Balconi & Pozzoli, 2009; Balconi & Lucchiari, 2006; Bekkedal et al., 2011; Knyazev et al., 2009), and to differentiate emotional stimuli based on their level of arousal (Aftanas et al., 2002; Balconi & Pozzoli, 2009; Balconi & Lucchiari, 2006; Balconi et al., 2009). Theta power is distributed within a large network of brain regions, appears to be involved in multimodal sensory and cognitive processing (Kowalczyk et al., 2013, Klimesch et al., 1999; for reviews see Karakaş, 2020 and Sauseng et al., 2010), and, consequently, is believed to have a role in orienting and processing of arousing stimuli (Aftanas et al., 2004; Karakaş, 2020). In particular, theta power is related to affective attention on perceptual processing of the stimulus (e.g., Zhang et al., 2013). Consistently, theta rhythm is prevalent in superficial cortical layers in a widely distributed fashion, supporting its role in the optimization of perceptual features in the environment (e.g., Halgren et al., 2015). In addition, theta connections encompass subcortical limbic structures, and this suggests that theta activity could embody corticolimbic pathways involved in the cognitive integration of emotional information (Hyman et al., 2005). In addition, theta dynamics during affective processing are characterized by two distinct stages: 1) an early peak occurring before 300ms post-stimulus that reflects automatic and unconscious orienting and 2) a later peak modulated by the conscious and intentional processing of the information (Knyazek et al., 2009). In this context, posterior late theta synchronization to emotional stimuli was found to be selectively reduced by distraction, suggesting that the second stage of theta dynamics can be deliberately modulated (Uusberg et al., 2014; Zhang et al., 2013; Figure 2.11).

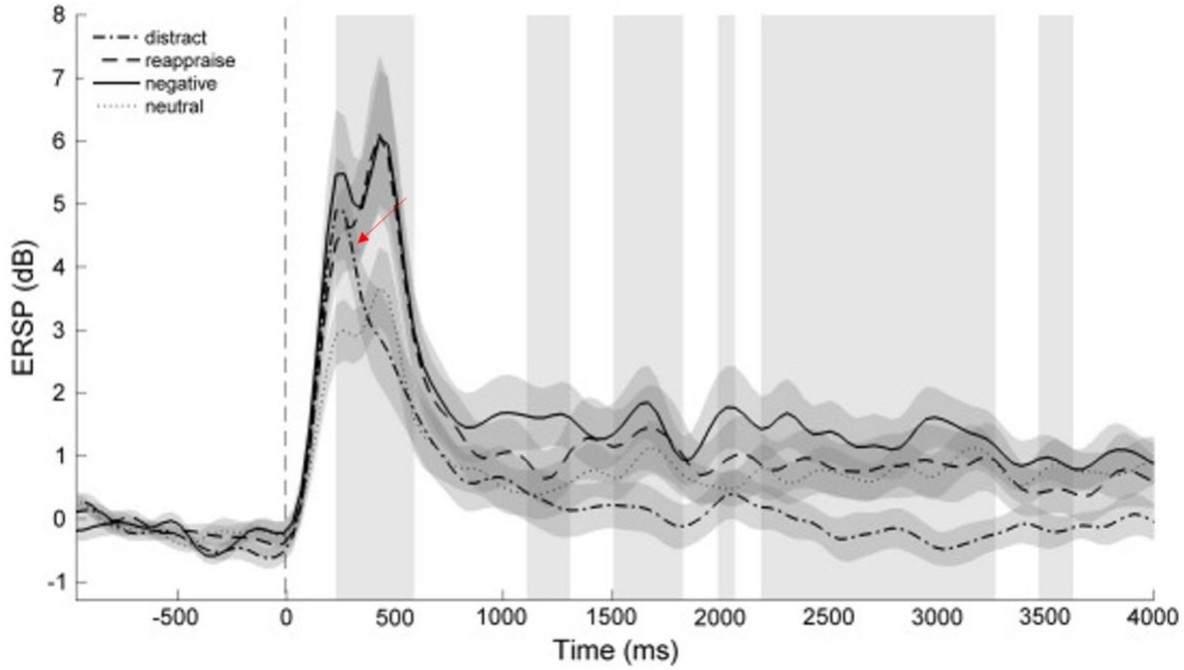

Figure 2.11 Theta power in a posterior cluster during the passive viewing of neutral and negative pictures, the reappraisal of negative pictures, and the distraction strategy from negative pictures. In the 350-550ms time window, theta power significantly decreased in the distraction (indicated by the red arrow) compared to reappraise and negative view condition. *Adapted from Uusberg et al., 2014.*

Only a small number of studies have examined theta oscillatory patterns during affective processing in depression or dysphoria. An early frontal (~ 200-250 ms) weaker theta in response to vocalized emotional cues (pleasant and unpleasant) was found in individuals with subclinical depressive symptoms (Slobodskoy-Plusnin, 2017). In this study, emotional categories were analyzed as a unitary group and the findings were interpreted as a deficit in the cognitive processing of all salient content. Accordingly, depressive symptoms are believed to be associated with reduced orienting and salience processing (Pardo et al., 2006). Moreover, reduced theta oscillations to pleasant cues and enhanced theta to unpleasant cues relative to neutral ones in individuals with dysphoria were observed, supporting the hypothesis of higher cognitive processing of unpleasant stimuli but reduced for pleasant ones in this group (Bocharov et al, 2017; Figure 2.12).

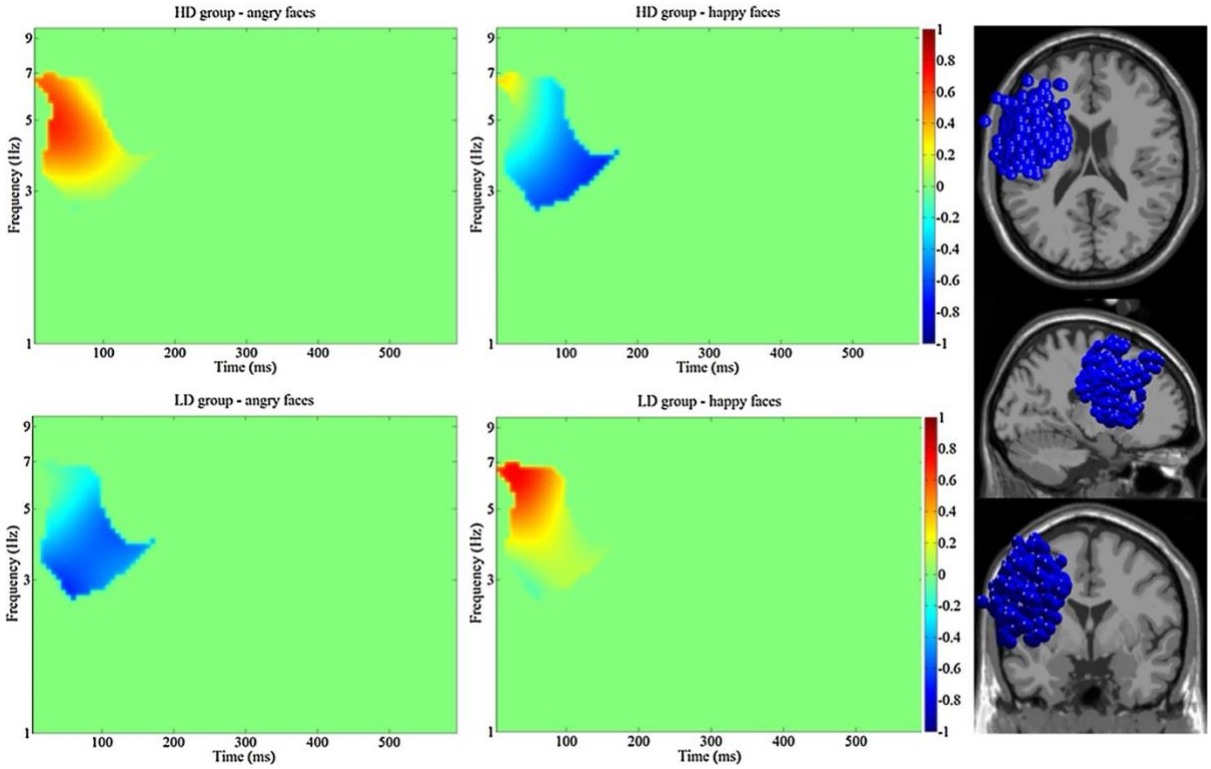

Figure 2.12 Time-frequency plots of average power (log dB) in a group with high depressive symptoms (HD, above) and a group with low depressive symptoms (LD, below) in response to angry (left) and happy (right) faces. Warmer colors indicate greater synchronization, while green areas are not significant. The LD group showed reduced theta to angry faces and increased theta to happy faces. The HD group showed the opposite pattern, with increased theta to angry faces and decreased theta to happy faces. The right panels show the localization of theta power, which was mostly in the left inferior frontal gyrus. *From Bocharov et al., 2017.*

Alpha activity (8 – 13 Hz), a measure considered to be inversely related to the level of cortical activation (Freeman & Quiroga, 2012), is thought to be an indicator of affective disposition (Davidson, 1998). The study of resting-state and event-related alpha activity has focused on frontal alpha asymmetry power (Güntekin & Başar, 2014). These studies have highly contributed to the motivational model of frontal asymmetry, which suggests that activity of the left frontal regions is associated with approach behavior, whereas the right frontal regions are involved in withdrawal from aversive stimuli (Davidson, 1988). Since alpha activity is an inverse index of cortical activity, the difference between left and right frontal alpha activity has been suggested to represent a measure of affective disposition (Allen et al., 2004).

Resting-state studies have correlated frontal alpha asymmetry with the balance of the two motivational systems, mood, and vulnerability for psychopathology (e.g., Davidson, 1998, 2004). For instance, reduced alpha at the left relative to right frontal sites has been correlated with reward responsiveness (De Pascalis et al., 2010), trait-positive affect (Alessandri et al., 2015; Tomarken et al., 1992), approach motivation (Harmon-Jones & Allen, 1997, 1998), and better emotional regulation (Jackson et al., 2003). On the other hand, greater alpha at the left relative to the right frontal sites has been related to withdrawal motivation (Sutton & Davidson, 1997), and negative affect (Jacobs & Snyder, 1996; Schaffer et al., 1983). The capability model put forward by Coan and colleagues (Coan et al., 2006; Coan & Allen, 2004) suggests that individual differences in frontal alpha asymmetry might be best detected during emotionally charged conditions. This model was built on a series of studies showing that even 10-months old infants (Davidson & Fox, 1982) had an increased left frontal activation (i.e., alpha desynchronization) in response to happy relative to sad facial expressions. Similarly, the voluntary production of happy facial expressions increased left frontal activation (Ekman & Davidson, 1993). Another study reported greater frontal left activity in response to the viewing of a sweet that was highly liked by participants and in participants that had not eaten for several hours (Harmon-Jones & Gable, 2009; Figure 2.13). Overall, these results support the hypothesis that left frontal activation reflects approach motivation. However, it appears that frontal asymmetric brain dynamics are not modulated by the valence of the context (i.e., pleasant vs. unpleasant) but by motivation tendencies. Indeed, state anger induced in multiple ways (by insulting participants, social rejection), increased left frontal activation compared to a non-anger state condition (Harmon-Jones & Sigelman, 2001; Harmon-Jones et al., 2009; Verona et al., 2009).

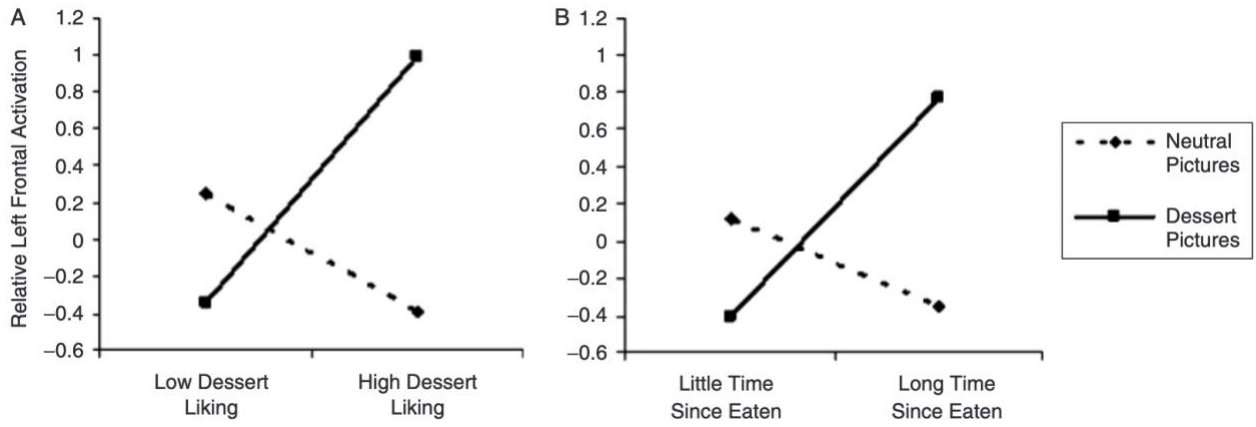

Figure 2.13 (Left panel) Interaction of liking for dessert and picture condition on relative left frontal activation during the picture viewing. (Right panel) Interaction of time since eaten and picture condition on left frontal activation during the entire picture viewing. *From Harmon-Jones & Gable, 2009.*

Depressive symptoms have been associated with an asymmetric pattern of resting-state alpha activity characterized by increased alpha in the left frontal cortex compared to the right, possibly reflecting the hypoactivation of the approach-related motivation system (Allen et al., 2004). To date, only a few studies have examined alpha asymmetry during emotional processing in dysphoria or depression (Mennella et al., 2015; Messerotti Benvenuti et al., 2019; Stewart et al., 2011; Stewart et al., 2014). Most of the studies have analyzed alpha activity only at anterior scalp sites, but a smaller alpha desynchronization (i.e., greater alpha) in frontal and right centro-parietal regions to pleasant images was recently found in dysphoria (Messerotti Benvenuti et al., 2019; Figure 2.14). Given that right parietal activity reflects arousal (Bruder et al., 2005; Stewart et al., 2011), these results were interpreted as an under-engagement of the approach-related motivational system in individuals with dysphoria.

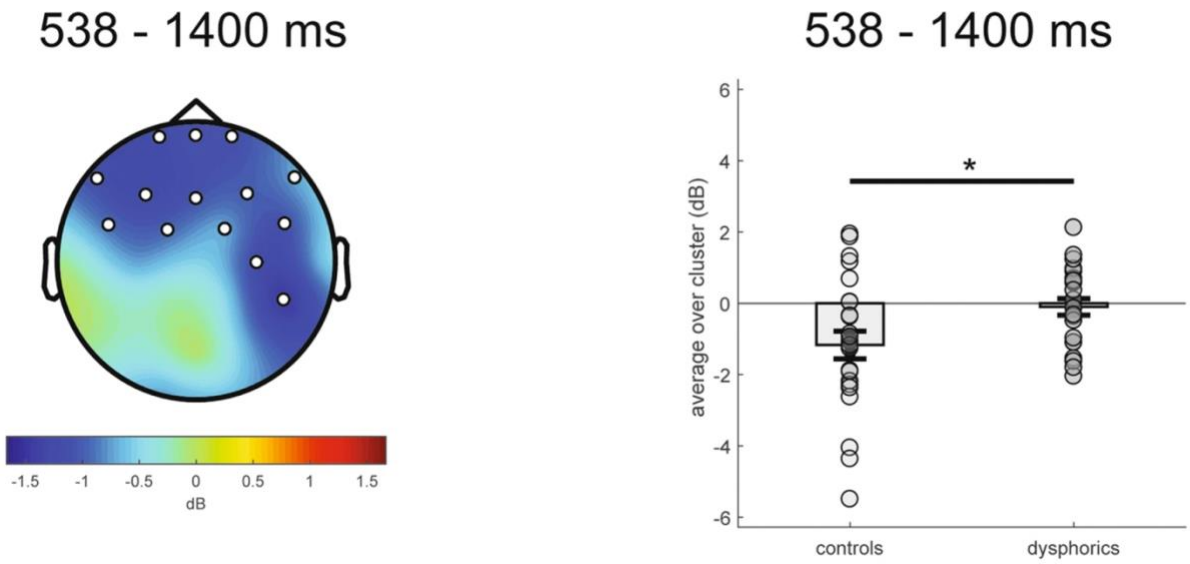

Figure 2.14 Time-frequency results for alpha power to pleasant images in subclinical depression and controls. Subclinical depression was related to reduced alpha desynchronization in frontal and right temporal regions to pleasant images relative to controls. (Left) Topography of the mean difference between groups in event-related alpha power (dB; group without dysphoria minus group with dysphoria) averaged over the significant time window for the pleasant condition. (Right) Mean event-related alpha power (dB) in the group with subclinical depression (dysphoria) vs. controls averaged over the significant electrodes and time points for the pleasant condition. *From Messerotti Benvenuti et al., 2019.*

Beta oscillations (13-30 Hz) are prevalent during states of wakefulness and arousal Kilner et al., 2005). In comparison with delta, theta, and alpha frequency bands, beta oscillations have been less subjected to examination during affective processing. However, recent findings suggest that beta desynchronization (i.e., suppression, reduction) could be a measure of motor preparation observed during motivational states (Gable et al., 2021). For instance, beta suppression and positive affect were greater before the achievement of a goal relative to after the goal attainment (Gable et al., 2021). This is in line with the hypothesis that approach-motivated pre-goal states tend to increase neural preparation and cognitive processes to facilitate goal pursuit (Gable et al., 2016; Wilhelm & Gable, 2021). Therefore, beta suppression may be an important indicator of motivated action.

Regarding affective picture-viewing tasks, beta power dynamics follow a specific pattern of early synchronization (0-100 ms) and later desynchronization (starting 200 ms post-stimulus) in response to emotional stimuli (Güntekin & Tülay, 2014; Jessen & Kotz, 2011;

Wright et al., 2012). A few studies suggested that this pattern could be modulated by emotional valence, showing that the initial parietal beta increase was higher for unpleasant relative to pleasant and neutral pictures (Güntekin & Basar, 2007; Güntekin & Tülay, 2014). Moreover, a recent study reported greater lower beta (12 – 20 Hz) power suppression over posterior regions during the processing of erotic (highly arousing) relative to romantic (less arousing) pictures (Schubring & Schupp, 2019). In another study, the same researchers reported greater beta power suppression over posterior regions to mutilation stimuli (highly arousing) relative to unpleasant but low-arousing pictures (Schubring & Schupp, 2021; Figure 2.15). Hence, beta power dynamics seem to be modulated by the arousal and not the valence of the context. To date, beta power during affective picture processing in depression remains unexplored.

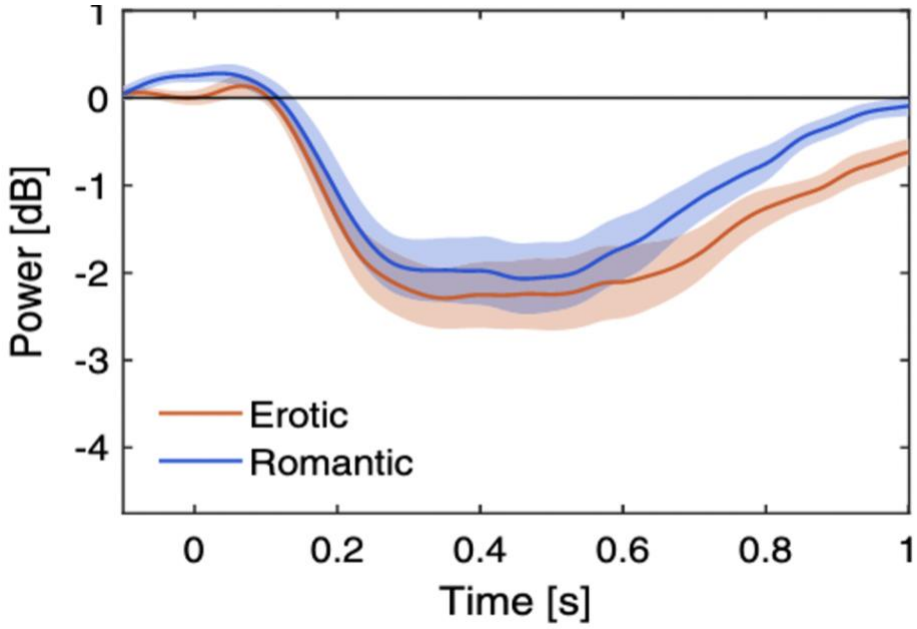

Figure 2.15 Time course of event-related desynchronization of lower beta (12-20 Hz) power for romantic (blue) and erotic (red) images. Erotic images (highly arousing) elicited greater desynchronization relative to romantic ones. *From Schubring & Schupp, 2019.*

Taken together, this Section reviewed the role of the main EEG oscillations in the processing of affective stimuli. This dissertation work was primarily aimed at exploring approach motivation and cognitive processing of emotional stimuli in subclinical and clinical depression and, in addition to ERPs, the exploration of different time-frequency patterns during affective picture processing represents a valuable method to disentangle these overlapping

mechanisms. On the one hand, from the reviewed literature, event-related delta power and alpha asymmetry to pleasant (relative to unpleasant and neutral) pictures could be the most promising measures to explore motivational aspects related to depressive symptoms. On the other hand, theta power might be employed to investigate the cognitive elaboration of affective and neutral visual cues. Overall, event-related oscillations to affective relative to neutral pictures can be employed to study the perceptual and cognitive processing of emotional information in relation to depressive symptoms.

PART II:

The experiments

CHAPTER III

STUDY 1: AFFECTIVE-COGNITIVE PICTURE PROCESSING IN DYSPHORIA: A TIME-DOMAIN AND TIME-FREQUENCY STUDY[2]

3.1 Abstract

As detailed in previous Chapters, to date, affective and cognitive processing of emotional information in individuals with depressive symptoms have been examined through peripheral psychophysiological measures, event-related potentials, and less frequently with time-frequency analysis of oscillatory activity. However, electrocortical correlates of emotional and cognitive processing of affective content in depression have not been fully defined. Time-frequency analysis of electroencephalographic activity allows disentangling the brain's parallel processing of information. The present study employed a time-frequency approach to simultaneously examine **affective disposition and cognitive processing** during the viewing of emotional stimuli in dysphoria. Time-frequency event-related changes were examined during the viewing of pleasant, neutral, and unpleasant pictures in 24 individuals with dysphoria and 24 controls. Affective disposition was indexed by delta and alpha power, and theta power was employed as a correlate of cognitive elaboration of the stimuli. The late positive potential (LPP) was also computed as a measure of sustained processing of motivationally salient stimuli. The group with dysphoria revealed a smaller LPP amplitude than the group without dysphoria in response to pleasant and neutral, but not unpleasant, stimuli at centro-parieto-occipital sites. Cluster-based statistics revealed a centro-parietal reduction in

[2] Results from this study have been published in **Dell'Acqua, C.,** Dal Bò, E., Moretta, T., Palomba, D., & Messerotti Benvenuti, S. (2022). EEG time–frequency analysis reveals blunted tendency to approach and increased processing of unpleasant stimuli in dysphoria. *Scientific Reports*, 12, 1-13 and Moretta, T., Dal Bò, E., **Dell'Acqua, C.,** Messerotti Benvenuti, S., & Palomba, D. (2021). Disentangling emotional processing in dysphoria: An ERP and cardiac deceleration study. *Behaviour Research and Therapy*, 147, 103985.

delta power for pleasant stimuli in individuals with dysphoria than controls. Also, dysphoria was characterized by an early fronto-central increase in theta power for unpleasant stimuli relative to neutral and pleasant. Comparatively, controls were characterized by a late fronto-central and occipital reduction in theta power for unpleasant stimuli relative to neutral and pleasant. The present study granted novel insights on the interrelated facets of affective elaboration in dysphoria, mainly characterized by a hypoactivation of the approach-related motivational system and a sustained facilitated cognitive processing of unpleasant stimuli. In terms of the RDoC dimensions, these results suggest a reduced functioning of the Positive Valence Systems as well as a potential interaction between the Negative Valence Systems and the Cognitive Systems in conferring depression risk.

3.2 Introduction

Ranked among the world's most common and economically burdensome conditions, depression is a mood disorder that results in sustained negative affect and/or loss of interest in pleasant activities (APA, 2013; Lim et al., 2012). Dysphoria is a condition characterized by depressive symptoms that does not meet the criteria for a formal diagnosis of major depression with respect to the frequency, duration and/or severity of symptoms (Rodríguez et al., 2021). Dysphoria is an acknowledged risk factor for the development of clinical depression measured at follow-up assessments of up to 4 years (e.g., Lee et al., 2019; Pietrzak et al., 2013). Studying dysphoria has several advantages, as it represents a risk condition for the onset of clinical depression, and it allows to analyze early depressive symptoms without any confounds provoked by the chronicity of the disorder or by the intake of antidepressant medications.

A core feature of depressive symptoms is dysregulated affective disposition (Fowles et al., 1988). Particularly, symptoms of sadness and distress have been linked to the activation of the withdrawal-related motivational system, which is primarily activated in contexts of threat

(Bradley et al., 2001). Conversely, symptoms of anhedonia, psychomotor retardation, and apathy are linked to the hypoactivation of the approach-related motivational system (Admon & Pizzagalli, 2015). Dysregulated affective disposition can be assessed by examining emotional responses, a multifaceted affective process involving subjective, behavioral, and physiological adjustments to affective experience (Lang et al., 1997). Of note, emotional responding has been widely studied in relation to the development and maintenance of depressive symptoms and three main hypotheses have been put forward (e.g., Rottenberg et al., 2005). Firstly, the negative potentiation hypothesis holds that negative mood tends to potentiate emotional responding to unpleasant stimuli, indicating a heightened activation of the withdrawal-related motivation system (e.g., Cook et al., 1992; Sigmon et al., 1992). Although this model is coherent with depression's feature of sustained negative affect, it is not fully supported by recent empirical evidence suggesting, instead, that depressed mood is mostly linked to a reduced emotional responding to positively valenced or rewarding stimuli (e.g., Rottenberg et al., 2005; Dunn et al., 2004; Forbes et al., 2012; Mennella et al., 2015; Messerotti Benvenuti et al., 2015; Messerotti Benvenuti et al., 2017; Messerotti Benvenuti et al., 2019; Klawohn et al., 2020). This second view, known as the positive attenuation hypothesis, holds that depressive symptoms are mostly linked to a reduced emotional response to pleasant content, indicating a hypoactivation of the approach-related motivational system in the brain (Forbes et al., 2012; Mennella et al., 2015, Messerotti Benvenuti et al., 2017; Messerotti Benvenuti et al., 2019; Klawohn et al., 2020; Bylsma et al., 2008). Notably, the hypoactivation of approach-related motivation represents an important risk factor for the development of depression (Admon & Pizzagalli, 2015; Luking et al., 2016) Moreover, within the Research Domain Criteria (RDoC matrix, Insel et al., 2010), is included a dimension believed to be a potentially unique feature contributing to depression, namely the hypoactivation of the Positive Valence System (Nusslock et al., 2015). The positive attenuation hypothesis has been extended

to a third alternative, the **emotional context insensitivity** (ECI) hypothesis (Bylsma et al., 2008; Bylsma, 2020), which holds that depression is characterized by a hypoactivation of both motivational systems (Rottenberg et al., 2005; Bylsma, 2020; Rottenberg & Hindash, 2015; Sloan & Sandt, 2010). Meta-analytic evidence provided support for a positive attenuation and the ECI model, but not for the negative potentiation hypothesis (Bylsma et al., 2008; Rottenberg & Hindash, 2015). Considering the dimensional approach provided by the RDoC outlined in Chapter I, the ECI model suggests a reduced functioning of both the Positive (PVS) and Negative (NVS) Valence Systems in depression and its risk.

In addition to dysregulated affective disposition, altered cognitive processes of affective content have been shown to play a critical role in the development and maintenance of depressive symptoms. Particularly, according to classical cognitive models of depression, negative self-referential schemata, characteristic of depression, affect cognitive processing and, particularly, attention (Clark et al., 1999) The facilitated processing of negative information is believed to contribute to the etiopathogenesis and maintenance of depressive symptoms (Beck & Bredemeier, 2016; Gotlib & Joormann, 2010; LeMoult & Gotlib, 2019). Compared to controls, individuals with depressed mood showed increased orienting and processing of negatively valenced stimuli (e.g., Disner et al., 2011; Koster et al., 2010; Moretta et al., 2021; Kaiser et al., 2018; for a review see Gotlib & Joormann, 2010). This mechanism has been suggested to generate a rigid pattern of negative appraisal of unpleasant events, which results in an increased difficulty to reappraise and regulate emotions (Disner et al., 2011; Kircanski et al., 2012). Further, depression appears also to be characterized by reduced processing of pleasant stimuli (e.g., Moretta et al., 2021; Shane & Peterson, 2007; for a review see Winer & Salem, 2016), indicating attentional avoidance of pleasant content.

To date, affective disposition and cognitive processing of affective content, two synchronous mechanisms, have been jointly examined through peripheral psychophysiological

measures or event-related potentials (ERPs) (e.g., Bradley et al., 2001; Codispoti et al., 2006; Messerotti Benvenuti et al., 2020). Indeed, ERPs have been largely employed to study affective stimuli processing in real-time during exposure to standardized emotional stimuli (Cuthbert et al., 2000; Palomba et al., 1997; Schupp et al., 2006). Specifically, as described in Chapter II, variability in Late Positive Potential (LPP) reflects reactivity to motivationally salient content, stimuli representation in short-term memory, and meaning evaluation (Bradley et al., 2003; Schupp et al., 2006). Specifically, the LPP is a positive and sustained shift reaching its maximum amplitude between 600 and 800 ms following the presentation of motivationally salient (pleasant and unpleasant) stimuli (Cuthbert et al., 2000; Schupp et al., 2000; Zhang et al.,2012).

Given the robust role of the LPP in discriminating emotional vs. neutral cues, researchers have been particularly interested in examining it in depression as a correlate of reactivity to pleasant and/or unpleasant content. To the best of our knowledge, only one study supported enhanced attention (reflected by a larger LPP amplitude) towards unpleasant stimuli (Benau et al., 2019), whereas a reduced LPP in response to threatening content was found in both depression (Foti et al., 2010; MacNamara et al., 2016; Weinberg et al., 2017) and risk for depression (Kujawa, et al., 2012). On the other hand, blunted LPP in response to pleasant stimuli has been found in depression (Grunewald et al., 2019; Klawohn et al., 2020; Weinberg et al., 2016; for a review see Proudfit et al., 2015), in children with depressive symptoms (Kujawa et al., 2011; Whalen et al., 2020) or at risk for depression (Levinson et al., 2018; Nelson et al., 2015), and to prospectively predict depression onset (Sandre et al., 2019). Taken together, these findings (i.e., reduction of LPP amplitude for pleasant and unpleasant images) support the prediction of the ECI model (Benning & Ait Oumeziane, 2017; Cavanagh & Geisler, 2006; Hill et al., 2019).

Nevertheless, an even more advantageous measure that can be employed is the **time-frequency analysis** of electroencephalographic (EEG) activity within specific frequency bands while participants are exposed to affective vs. neutral content. Indeed, time-frequency analysis allows the extrapolation of information that is not available using ERPs analysis and reflects distinctive aspects of information processing (e.g., Herrmann et al., 2014). Specifically, affective disposition can be assessed by analyzing delta (1-3 Hz) and alpha (8-12 Hz) frequency bands. Although delta oscillations are considered a correlate of cortical inactivation prominent during sleep (Dang-Vu et al., 2008), recent studies have demonstrated that delta rhythm across spatially distributed cortical regions sustains basic motivational drives, especially towards pleasant and rewarding stimuli (Knyazev, 2011). Indeed, delta oscillations appear to have a functional role in monitoring the motivational relevance of affective cues and in the identification of pleasant/rewarding stimuli and are generated by subcortical regions involved in the motivational system (Knyazev, 2011; Knyazev, 2007; Alper et al., 2006; Foti et al., 2015). Studies have shown that event-related delta power is increased by emotionally salient cues (unpleasant and pleasant) as compared to neutral ones mostly in centro-parietal regions (Balconi et al., 2009; Knyazev, 2011; Zhang et al., 2013). However, to date, delta power in individuals with depressive symptoms during a picture viewing task has not been fully explored. Furthermore, alpha band, a measure considered to be inversely related to the level of cortical activation (Freeman & Quiroga, 2012), is thought to be an indicator of affective disposition (Davidson, 1998). An asymmetric pattern of alpha activity, with increased alpha in the left frontal lobe compared to the right, reflects a hypoactivation of the approach-related motivation system and has long been considered to represent a potential biomarker for depression in resting-state conditions (Davidson, 1998; Allen et al., 2004; for a review see Van Der Vinne et al., 2017) and even more in emotional contexts (Coan et al., 2006). However, to date, only a few studies have examined alpha asymmetry during emotional processing in

dysphoria or depression (Mennella et al., 2015; Messerotti Benvenuti et al., 2019; Stewart et al., 2011; Stewart et al., 2014). Also, most studies have analyzed alpha activity only at anterior scalp sites, even if asymmetry in the alpha in depression has also been reported at posterior scalp sites. Indeed, individuals with or without familiarity for depression showed a right temporo-parietal dysfunction, as indexed by higher alpha activity (Messerotti Benvenuti et al., 2019; Stewart et al., 2011). Particularly, a smaller alpha desynchronization (i.e., higher alpha) in frontal and right centro-parietal regions to pleasant images was found in dysphoria (Messerotti Benvenuti et al., 2019). Given that right parietal activity is thought to reflect arousal (Stewart et al., 2011; Bruder et al., 2005), these results were interpreted as an under-engagement of the approach-related motivational system in individuals with dysphoria.

Furthermore, theta band (4-8 Hz) reflects the processing of salient events and can be employed to assess cognitive processing during the viewing of affective content (Siegel et al., 2000). Specifically, theta, distributed within a large network of brain regions involved in multimodal sensory and cognitive processing (Kowalczyk et al., 2013; Klimesch, 1999; for reviews see Karakaş, 2020 and Sauseng et al., 2010), is believed to have a role in orienting and processing of arousing stimuli (Karakaş, 2020; Aftanas et al., 2004). Congruently, theta oscillations are prevalent in superficial cortical layers in a widespread distributed fashion, supporting its role in the optimization of perceptual features in the environment (e.g., Halgren et al., 2015). Moreover, considering that theta connections encompass subcortical limbic structures, theta activity could embody corticolimbic pathways involved in the cognitive integration of emotional information (Hyman et al., 2005). As a matter of fact, a greater event-related theta power for affective vs. neutral pictures at bilateral fronto-posterior sites was reported (e.g., Balconi & Lucchiari, 2006; Balconi et al., 2009) and was suggested to reflect the role in the integration of affective and cognitive aspects of attentional operations (Knyazev, 2007; Knyazev et al., 2009). To date, only a few studies have examined theta during affective

processing in individuals with depression or dysphoria. An early frontal (~ 200-250 ms) weaker theta in response to vocalized emotional cues was reported in individuals with depressed mood (Slobodskoy-Plusnin, 2018). Despite emotional categories were analyzed as a unitary category, this pattern was interpreted as a deficit in cognitive processing of all salient content (Slobodskoy-Plusnin, 2018). Accordingly, depressive symptoms are believed to be associated with reduced orienting and salience processing (Pardo et al., 2006). Further, Reduced theta oscillations to pleasant cues and enhanced theta to unpleasant cues relative to neutral ones in individuals with dysphoria were observed, suggesting higher cognitive processing of unpleasant stimuli but reduced for pleasant ones in this group (Bocharov et al., 2017).

The present study aimed to **simultaneously examine affective disposition and cognitive processing in individuals with dysphoria** through the analysis of time-frequency changes within delta, theta, and alpha bands during the passive viewing of pictures from the International Affective Picture System (IAPS) library (Lang et al., 2008). Additionally, the LPP was also analyzed to assess motivational salience elicited by the emotional pictures relative to neutral ones.

The formulated hypothesis was twofold and was based on the abovementioned functional correlates of delta, theta and alpha bands. First, regarding affective disposition, the dysphoria group was expected to show a hypoactivation of the approach-related motivational system and, as suggested by the ECI model, a potential hypoactivation of the withdrawal-related motivational system. Specifically, the group with dysphoria was expected to show a smaller LPP and smaller increase in delta band activity in response to pleasant and unpleasant vs. neutral pictures across spatially distributed cortical regions relative to controls. Also, considering that reviewed evidence supporting the role of alpha as a measure of the approach-related motivational system, the dysphoria group was expected to show a smaller alpha desynchronization in the left frontal and right parietal cortex in response to pleasant (but not

neutral and unpleasant) stimuli relative to controls. Second, regarding cognitive processing, a facilitated cognitive processing of unpleasant and reduced processing of pleasant stimuli was expected in the group with dysphoria. Namely, these processing patterns would be indexed by increased theta activity to unpleasant relative to neutral stimuli and to controls and by a reduced theta activity to pleasant relative to neutral pictures and relative to controls.

3.3 Methods

Participants

A cohort of 85 Caucasian students at the University of Padua, Italy, voluntarily took part in the research project. The sample was medically healthy and free from psychotropic medication, as assessed with an ad-hoc anamnestic interview. In the present study, a group with dysphoria and a group without dysphoria were identified on specific criteria. Participants with dysphoria were identified by module A of the Structured Clinical Interview for DSM-5 (SCID 5-CV; First et al., 2016; Italian version Fossati & Borroni, 2017) assessing current and past depressive symptoms. Furthermore, the Beck Depression Inventory-II (BDI-II, Beck et al., 1996; Ghisi et al., 2006) was also employed for the assessment of depressive symptoms' severity. Based on the psychological assessment, 27 participants (5 males) who scored equal to or greater than 12 on the BDI-II and showed at least two present depressive symptoms, for at least two weeks, without meeting the diagnostic criteria for major depression, persistent depressive disorder, or bipolar disorder, were assigned to the group with dysphoria. Twenty-five participants (12 males) who scored equal to or lower than 8 on the BDI-II and had no history of depression or current depressive symptoms were assigned to the control group (i.e., without dysphoria). To ensure separation between groups with dysphoria and without dysphoria, participants who scored between 9 and 11 on the BDI-II were excluded from the present study (n = 17). Also, individuals without depressive symptoms but with at least one

past depressive episode (i.e., remitted, see Dell'Acqua et al., 2020) were excluded from the present study (n = 16).

With respect to demographic variables, the two groups included in the analyses (with dysphoria, without dysphoria) did not differ in terms of age (p = .645; dysphoria group: Mean (M) = 20.7, standard deviation (SD) = 2.56, min = 18, max = 24; group without dysphoria: M = 20.4, SD = 1.72, min = 18, max = 28), sex ($\chi 2$ =3.375, p =.066), and education (p = .920; dysphoria group: M = 15.0, SD = 1.56, min = 14, max = 18; group without dysphoria: M = 15.0, SD = 1.30, min = 14, max = 17).

Participants were given 13 € for their participation. All participants read, understood, and signed informed consent. The research was conducted in compliance with the World Medical Association Declaration of Helsinki on research on human subjects and was approved by the Ethical Committee of Psychological Research, Area 17, University of Padua (prot. no. 3612).

Psychological measures

The Italian version of the mood episode module (module A) of the SCID-5-CV was employed as a reliable tool to assess the presence of dysphoria and to exclude individuals with major depression, persistent depressive disorder, or bipolar disorder. The SCID-5-CV was administered by a trained psychologist who had previous experience with administering structured clinical interviews. The Italian version of the BDI-II was also employed as a reliable measure of the severity of depressive symptoms in the past two weeks. It is a self-report questionnaire composed of 21 items, each with a Likert scale of four-points and scores range from 0 to 63, where higher scores indicating greater depressive symptoms. In the Italian version, a score of 12 has been reported as the optimal cut-off score to discriminate between individuals with and without depressive symptoms (Ghisi et al., 2006).

Experimental task and procedure

Twenty-four pleasant (e.g., erotic couples, sports), 24 neutral (e.g., household objects, neutral faces), and 24 unpleasant (e.g., attacking humans and animals) color pictures (600 × 800 pixels) were presented to participants. Highly arousing pleasant and unpleasant pictures were selected from the International Affective Picture System (IAPS; Lang et al., 2008) since these have been observed to induce elevated psychophysiological changes (e.g., Bradley et al., 2001). Pleasant and unpleasant pictures were matched for normative arousal ratings which were significantly higher than for neutral pictures. The number of the selected IAPS pictures are listed in the supplementary material.

Pictures were shown for 6000 ms each in a semi-randomized sequence (i.e., no more than one stimulus in the same emotional condition had to be shown consecutively). Each picture was preceded by a 3000 ms interval where a white fixation cross was placed centrally on a grey screen. Participants were required to look at the central fixation cross and keep their gaze on the center of the screen. Picture presentation was followed by a variable intertrial interval (ITI) of 6000–8000 ms, during which a white fixation cross (identical to the 3-sec baseline) was presented.

Before the experimental session, participants were required to avoid alcohol consumption the day before and to avoid caffeine and nicotine the same day of the appointment. Upon arrival at the laboratory, after reading and signing written informed consent, participants were administered the ad-hoc anamnestic interview, the mood episode module (module A) of the SCID-5-CV, and the BDI-II. Then, participants were seated on a comfortable chair in a dimly lit, sound-attenuated room. After electrodes attachment and a 3-minute resting-state period, six practice trials including two pleasant, two neutral, and two unpleasant pictures were provided. Then, participants underwent the emotional passive viewing task while EEG and electrocardiogram (ECG) were recorded (data from the ECG analyses are not presented here

but can be found in Moretta et al., 2021). At the end of the passive viewing task, 36 pictures (12 for each emotional category) were presented again, and ratings of emotional valence and arousal were obtained using a computerized version of the 9-point Valence and Arousal scales of the Self-Assessment Manikin (SAM; Bradley & Lang, 1994). Following the completion of the self-evaluation of emotional valence and arousal, participants were fully debriefed. The entire procedure lasted approximately 90 min. Figure 3.1 illustrates the experimental procedure.

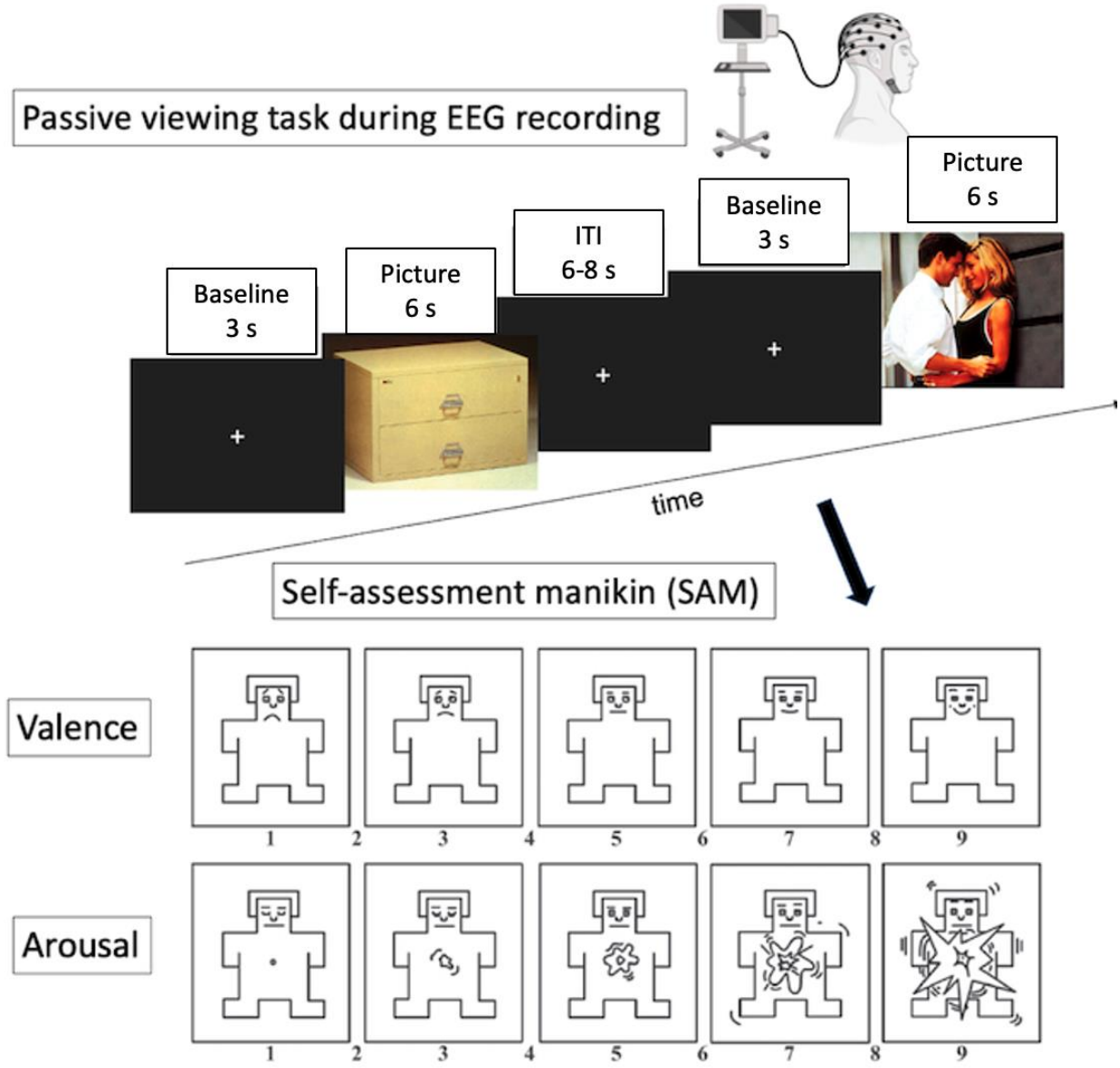

Figure 3.1 illustration of the passive viewing task and self-assessment manikin.

EEG recording

EEG data acquisition was accomplished using a computer running Eego software and using an Eego amplifier (ANT Neuro, Enschede, Netherlands). EEG was recorded using an elastic cap with 32 tin electrodes arranged according to the 10–20 System (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, POz, O1, Oz, O2, and mastoids: M1, M2), referenced online to CPz. Both vertical and

horizontal electrooculograms (EOGs) were recorded using a bipolar montage to monitor eye movements and eye-blinks. The electrode pairs were placed at the supra- and suborbit of the right eye and at the external canthi of the eyes, respectively. Electrode impedance was kept below 10 kΩ. The EEG and EOG signals were amplified with Eego amplifier (ANT Neuro, Enschede, Netherlands), bandpass filtered (0.3–40 Hz), and digitized at 1000 Hz.

EEG data reduction and analysis

The EEG signal was downsampled to 500 Hz and re-referenced offline to a linked mastoids montage as implemented in EEGLAB (Delorme & Makeig, 2005). Further processing was conducted in Brainstorm (Tadel et al., 2011). The EEG was filtered offline with a band-pass filter of 0.3-30 Hz and manually corrected for blink artifacts using independent component analysis (ICA). The EEG was then segmented into 6,000 epochs, from 3,000 ms before the stimulus onset to 3,000 ms after the stimulus onset, to prevent boundary effects (Messerotti Benvenuti et al., 2017). Each epoch was baseline-corrected by subtracting the mean pre-stimulus voltage between −250 ms and −50 ms. Segments that contained residual artifacts exceeding ±70 μV (peak-to-peak) were excluded. By applying the a priori criteria of excluding individuals for whom more than 50% of trials were rejected, two participants (2 females) in the group with dysphoria were excluded due to excessive noise on the EEG recording and failed mastoid, respectively. Moreover, one participant in the group with dysphoria (1 female) and one in the group without dysphoria (1 male) were excluded due to excessive noise on electrode T7 and overall low-quality signal which precluded cluster-based time-frequency analysis. On the remaining sample, the artifact rejection led to an average ± SD acceptance of 19.0 ± 3.6 pleasant trials, 18.5 ± 3.0 neutral trials, and 19.1 ± 3.2 unpleasant trials in the dysphoria group, and of 18.7 ± 3.2 pleasant trials, 18.7 ± 3.2 neutral trials, and 19.0 ± 3.1 unpleasant trials in the control group. No statistically significant differences between groups or among emotional

conditions in the average acceptance of pleasant, neutral, and unpleasant trials emerged (all *p*s >.15).

Time-frequency analysis

Time-frequency analysis was performed using Morlet wavelet transformation on individual trials for each 1-Hz frequency bin between 1 and 30 Hz, using a mother wavelet at 1 Hz with 3-s time resolution (full width at half maximum; FWHM). Time-frequency decompositions were then averaged for each participant and emotional condition, and the event-related spectral perturbation (ERSP) was computed as the change in power expressed in decibels (dB) relative to the baseline (−900 to −400 ms) in each frequency bin at each time point (Messerotti Benvenuti et al., 2019). Then, data were grand averaged across each group for each emotional condition.

Statistical analysis

Valence and arousal self-report ratings were submitted to separate linear mixed-effect models (LMMs), with participants as random term, and Category (pleasant, neutral, unpleasant) and Group (with dysphoria, without dysphoria) as fixed factors.

For both time-domain and time-frequency analyses, a cluster-based approach has been conducted to control over type I error rate arising from multiple comparisons across electrodes and time points (Maris & Oostenveld, 2007).

This approach is advantageous as it does not rely on assumptions about the distribution of the data or the theoretical underlying distribution of test statistics under the null hypothesis (i.e., Gaussian). Instead, the distribution is generated by the data itself, by iteratively shuffling the condition labels over trials (i.e., within-subjects) or over subjects (i.e., between-subjects) and recomputing the statistics. The shuffling is repeated thousands of times until a distribution

of the test statistic value observed under the null hypothesis is generated. If the observed statistic value (i.e., the test statistic associated with the non-shuffled data) falls within the distribution of the null-hypothesis test statistic values, the null hypothesis cannot be rejected and this would indicate that the observed data could have been randomly generated (Cohen, 2014; Luck, 2014b). Cluster-based correction assumes that a true effect should show a temporal and spatial extension, with neighbor sensors showing similar patterns (Cohen, 2014). With cluster-based correction, at each iteration of the null- hypothesis distribution generation, a threshold is applied to the time–frequency map, such that the outcome is units of clusters instead of single pixels (i.e., electrodes). In the present study, once thresholded values resulted from statistics across electrodes and time points were obtained, the differences within emotional conditions or between groups were shuffled pseudo-randomly 2000 times (Messerotti Benvenuti et al., 2019). To obtain a 'null' distribution of effect sizes, the maximal cluster-level statistics (i.e., the sum of values across contiguously significant electrodes and time points at the threshold level) were extracted for each shuffle. For each significant cluster in the (non-shuffled) data, the cluster-corrected *p*-value was computed as the statistics of the proportion of clusters in the null distribution that exceeded the one obtained for the cluster in question (Messerotti Benvenuti et al., 2019). The analysis was conducted with a − 100 to 1400 ms time window and clusters with a $p\text{corr} < .05$ were considered statistically significant.To test within-group differences in event-related power changes among emotional categories (pleasant, neutral, unpleasant) and between-group (with dysphoria, without dysphoria) differences within each emotional category, cluster-based repeated measures ANOVAs and two-tailed unpaired *t*-tests were employed, respectively. The cluster-based statistical tests were run on event-related potentials (ERPs), event-related delta (1–3 Hz), theta (4–7 Hz), and alpha (8–13 Hz) power over time-points in the −100 to 1400 ms interval and a $p < .05$ criterion was employed to threshold the matrices (Messerotti Benvenuti et al., 2019).

Further statistical analyses were conducted using a two-tailed α = .05. LPP and time-frequency power were extracted according to the significant time window and location (i.e., sensors) that emerged from the cluster-based between-group differences for pleasant pictures.

3.4 Results

Valence and arousal self-report ratings

The Category main effect was statistically significant for both valence and arousal ratings (valence: $F(2,150) = 201.13$, $p < .001$; arousal: $F(2,150) = 187.81$, $p < .001$). Unpleasant pictures were rated as significantly more unpleasant and arousing than pleasant and neutral pictures (all *p*s < .01). Moreover, pleasant pictures were rated as significantly more pleasant and arousing than neutral pictures (*p*s < .001). No significant main effect for Group or Group × Category interaction was found.

Event-related potentials (ERPs)

Differences among emotional categories in ERPs. The cluster-based analysis on ERP data showed a significant centro-parieto-occipital cluster (electrodes = CP5, CP1, CP2, CP6, P7, P3, PZ, P4, P8, POZ) in the group without dysphoria (cluster *F*-valuemax = 11249.33, *p*corr = .001, time window = 450–642 ms), and in the group with dysphoria (cluster *F*-valuemax = 26475.67, *p*corr < .001, time window = 352–700 ms), as shown in Figures 3.2 and 3.3, respectively. Particularly, both groups revealed a significantly larger LPP amplitude in response to pleasant and unpleasant stimuli than neutral ones (all *p*s < .01; Fig. 3.1 and 3.2).

Differences between groups in ERPs for each emotional category. Cluster-based unpaired *t*-tests revealed a significant positive centro-parieto-occipital cluster (electrodes = CP5, CP1, CP2, CP6, P7, P3, PZ, P4, P8, POZ) for the difference between the groups in response to pleasant (cluster *t*-valuemax = 963.16, *p*corr = 0.03, time window = 402–518 ms, Cohen's $d = -0.68$) and neutral (cluster *t*-valuemax = 1219.05, *p*corr = 0.02, time window =

396–550 ms, Cohen's $d = -0.74$) conditions, as shown in Figures 3.4 and 3.5, respectively. Specifically, individuals with dysphoria showed a significantly smaller LPP amplitude in response to both pleasant and neutral stimuli than those without dysphoria.

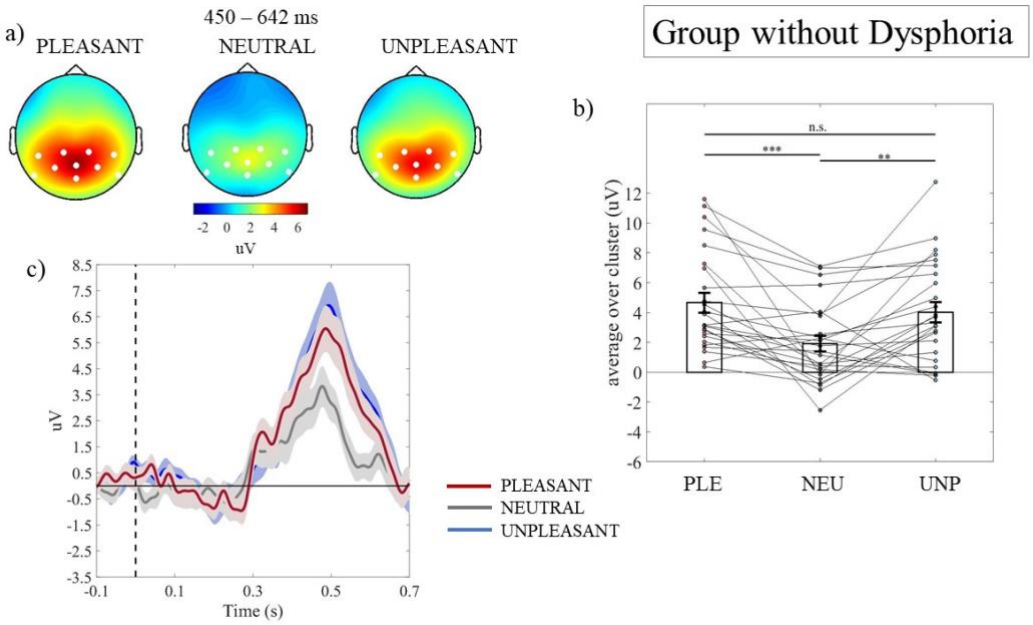

Figure 3.2 (Panel a) Topography of the mean ERP amplitude (μV) of individuals without dysphoria averaged over the significant time points (450-642 ms time window) for pleasant, neutral, and unpleasant conditions. (Panel b) Mean ERP amplitude of each participant averaged over the significant electrodes and time points for pleasant, neutral, and unpleasant conditions. Each circle represents one participant; black frames represent the mean ERP amplitude across all participants and the solid black lines represent ± standard error of the mean (SEM). $^{**}p < .01$; $^{***}p < .001$. (Panel c) Time course of grand-average ERP waveforms averaged over the significant electrodes for pleasant (red line), neutral (grey line), and unpleasant (blue line) conditions. Shaded areas represent ± SEM.

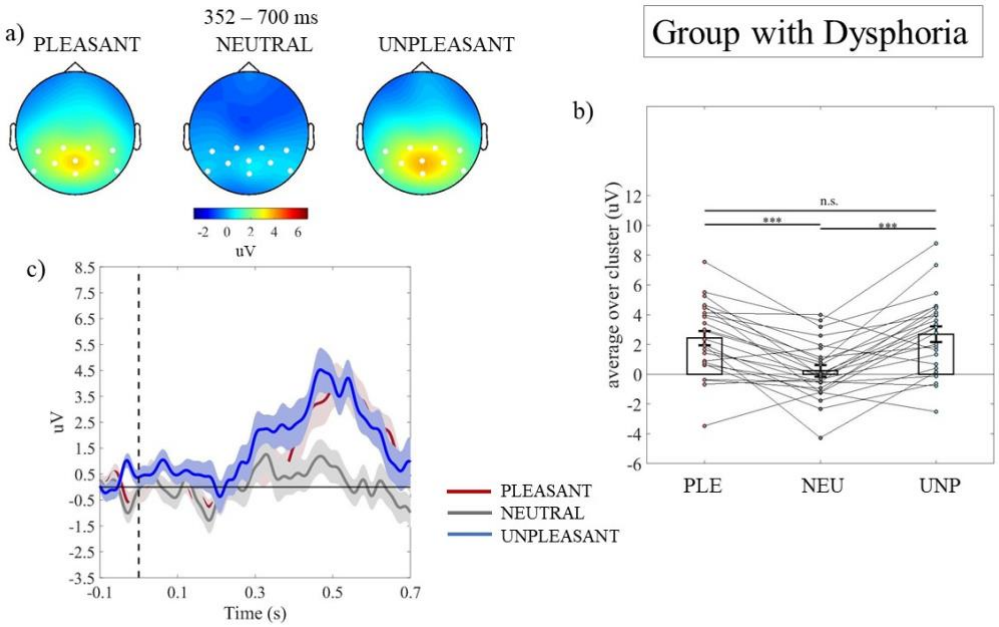

Figure 3.3 (Panel a) Topography of the mean ERP amplitude (μV) of individuals with dysphoria averaged over the significant time points (352-700 ms time window) for pleasant, neutral, and unpleasant conditions. (Panel b) Mean ERP amplitude of each participant averaged over the significant electrodes and time points for pleasant, neutral, and unpleasant conditions. Each circle represents one participant; black frames represent the mean ERP amplitude across all participants and the solid black lines represent ± SEM. ***$p < .001$. (Panel c) Time course of grand-average ERP waveforms averaged over the significant electrodes for pleasant (red line), neutral (grey line), and unpleasant (blue line) conditions. Shaded areas represent ± SEM.

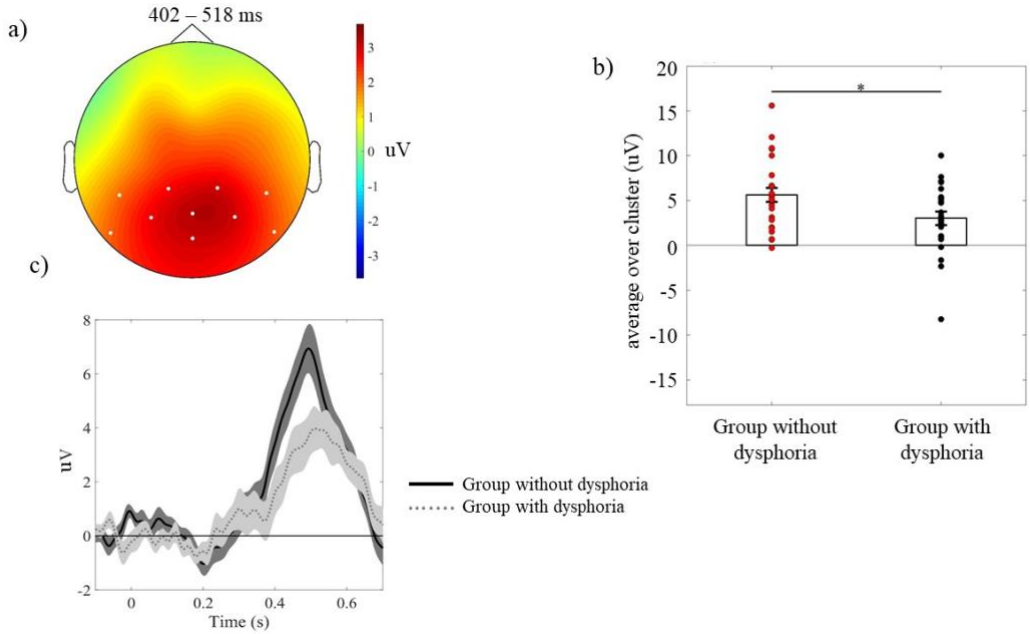

Figure 3.4 (Panel a) Topography of the mean difference between groups in mean ERP amplitude (μV; group without dysphoria minus group with dysphoria) averaged over the significant time points (402–518 ms time window) for the *pleasant condition*. (Panel b) Mean ERP amplitude of each participant in the group with dysphoria and the group without dysphoria averaged over the significant electrodes and time points for the pleasant condition. Each circle represents one participant; the frames represent the mean ERP amplitude across all participants in the group with dysphoria and in the group without dysphoria and the solid black lines represent ± SEM. *$p < .05$. (Panel c) Time course of grand-average ERP waveforms averaged over the significant electrodes for the pleasant condition in the group with dysphoria (dashed, light gray line) and in the group without dysphoria (solid black line). Shaded areas represent ± SEM.

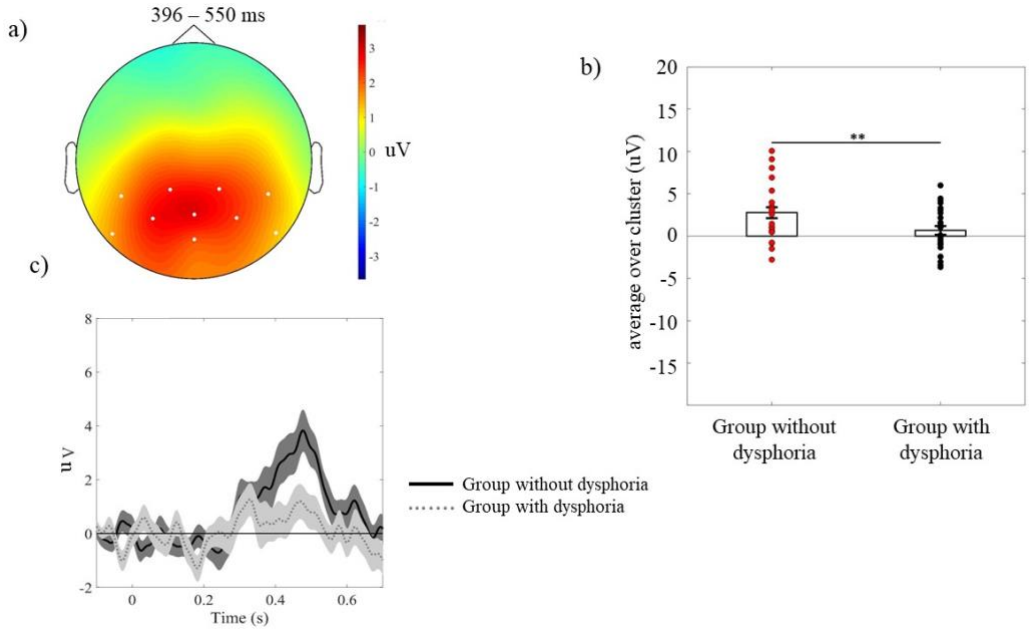

Figure 3.5 (Panel a) Topography of the mean difference between groups in mean ERP amplitude (μV; group without dysphoria minus group with dysphoria) averaged over the significant time points (396–550 ms time window) for the *neutral condition*. (Panel b) Mean ERP amplitude of each participant in the group with dysphoria and the group without dysphoria averaged over the significant electrodes and time points for the neutral condition. Each circle represents one participant; the frames represent the mean ERP amplitude across all participants in the group with dysphoria and in the group without dysphoria and the solid black lines represent ± standard error of the mean (SEM). ** $p < .01$. (Panel c) Time course of grand-average ERP waveforms averaged over the significant electrodes for the neutral condition in the group with dysphoria (dashed, light gray line) and in the group without dysphoria (solid black line). Shaded areas represent ± SEM.

Delta power

Differences among emotional categories in event-related delta power. The cluster-based analysis on event-related delta power showed a significant positive topographically widely distributed cluster in the group without dysphoria (electrodes = F3 FZ FC5 FC1 T7 C3 CZ CP5 CP1 CP2 CP6 P7 P3 PZ P4 P8 POZ; cluster $F\text{-value}_{max} = 67817.30$, $p_{corr} = .01$, time window = -100 - 898 ms), and in the group with dysphoria (electrodes = FP1 FPZ FP2 F7 F3 FZ F4 FC5 FC1 FC2 T7 C3 CZ C4 CP5 CP1 CP2 CP6 P7 P3 PZ P4 P8 POZ O1 OZ O2; cluster $F\text{-value}_{max} = 278357.09$, $p_{corr} = .001$, time window = -100 - 1400 ms) as shown in Figures 3.6 and 3.7, respectively. Both groups showed significantly greater delta to pleasant and unpleasant stimuli relative to neutral ones (all $ps \leq .017$).

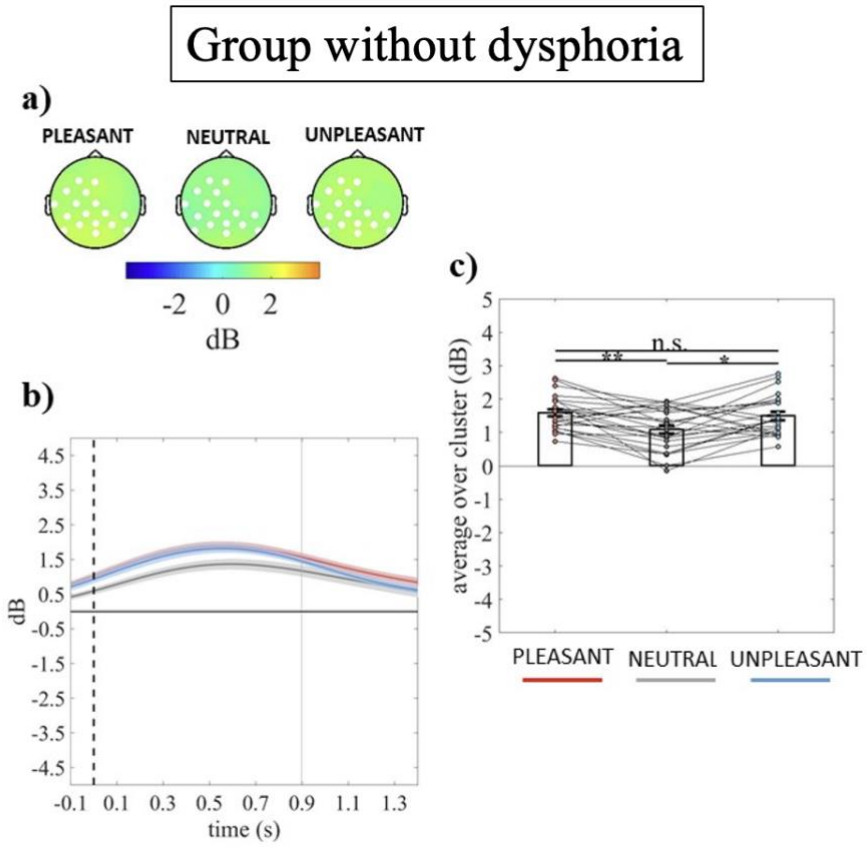

Figure 3.6 (Panel a) Topography of the mean event-related delta power [dB] of individuals without dysphoria averaged over the significant time points [-100 - 898 ms time window] for pleasant, neutral, and unpleasant conditions. (Panel b) Time course of grand-average event-related delta power of individuals without dysphoria averaged over the significant electrodes for pleasant [red line], neutral [grey line], and unpleasant [light blue line] conditions. Shaded areas represent ± standard error of the mean [SEM] and the gray line represents the end of the significant time window [898 ms]. (Panel c) Mean event-related delta power of each participant [in the group without dysphoria] averaged over the significant electrodes and time points for pleasant, neutral, and unpleasant conditions. Each circle represents one participant; colored frames represent the mean event-related delta power across all participants and the solid black lines represent ± SEM. *$p < .05$; **$p < .01$.

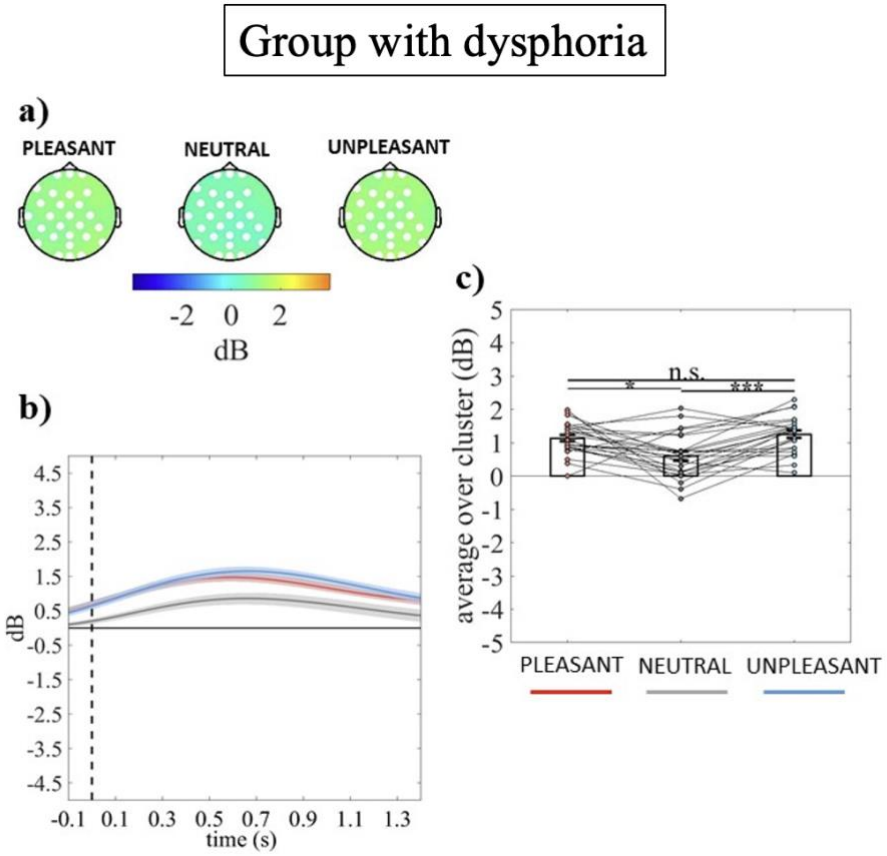

Figure 3.7 (Panel a) Topography of the mean event-related delta power [dB] of individuals with dysphoria averaged over the significant time points [-100 - 1400 ms time window] for pleasant, neutral, and unpleasant conditions. (Panel b) Time course of grand-average event-related delta power of individuals with dysphoria averaged over the significant electrodes for pleasant [red line], neutral [grey line], and unpleasant [light blue line] conditions. Shaded areas represent ± SEM. (Panel c) Mean event-related delta power of each participant [in the group with dysphoria] averaged over the significant electrodes and time points for pleasant, neutral, and unpleasant conditions. Each circle represents one participant; colored frames represent the mean event-related delta power across all participants and the solid black lines represent ± SEM. *$p < .05$; ***$p < .001$.

Differences between groups in event-related delta power for each emotional category.

Cluster-based unpaired *t*-tests on event-related delta power revealed significant positive clusters for the difference between the two groups within pleasant (electrodes = T7 CZ CP5 CP1 P7 P3 PZ P4 POZ O1 OZ; cluster $t\text{-value}_{max} = 14504.83$, $p_{corr} = .03$, time window = -100 - 1148 ms) and neutral (electrodes = FP1 FPZ F7 FZ FC5 FC1 FC2 FC6 C3 CZ C4 T8 CP1 CP2 CP6 P7 P3 PZ P4 P8 POZ O1 OZ O2; cluster $\text{t-value}_{max} = 24222.04$, $p_{corr} = .02$, time window = -100 - 958 ms) conditions, as shown in Figure 3.8. Specifically, the dysphoria group showed reduced delta in response to both pleasant and neutral stimuli relative to the group

without dysphoria. Unpaired *t*-test did not reveal any significant cluster for the difference between the groups within the unpleasant condition. Moreover, delta power within the significant clusters that emerged from the between-groups comparisons was not influenced by sex (neutral cluster, $p = .125$; pleasant cluster, $p = .270$).

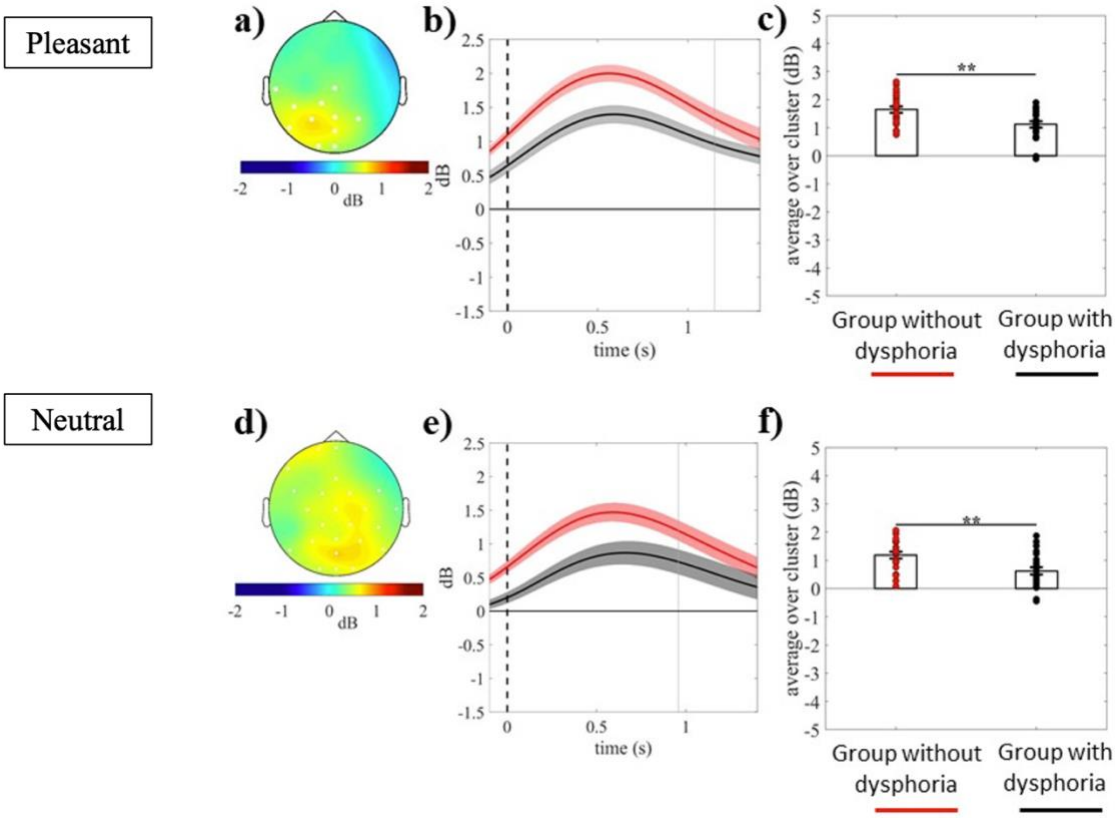

Figure 3.8 (Panels a and d) Topography of the mean difference between groups in event-related delta power [dB; group without dysphoria minus group with dysphoria] averaged over the significant time points for the pleasant (Panel a; -100 - 1148 ms time window) and (Panel d; -100 - 958 ms time window) neutral condition, respectively. (Panel b) Time course of grand-average event-related delta power averaged over the significant electrodes for pleasant and (Panel e) neutral conditions in the group with dysphoria [black line] and the group without dysphoria [red line]. Shaded areas represent ± SEM; the gray line represents the end of significant time windows. (Panel c) Mean event-related delta power of each participant in the group with dysphoria and the group without dysphoria averaged over the significant electrodes and time points for the pleasant condition and (Panel f) neutral condition. Each circle represents one participant; the frames represent the mean event-related delta power across all participants in the group with dysphoria and the group without dysphoria and the solid black lines represent ± SEM. $^{**}p < .01$.

Theta power

Differences among emotional categories in event-related theta power. The cluster-based analysis on event-related theta power showed a significant positive fronto-centro-

parieto-occipital cluster in the group without dysphoria (electrodes = FP1 FPZ FP2 FZ F4 F8 FC1 FC2 FC6 CZ T8 CP1 CP2 CP6 P7 P3 PZ P4 POZ O1 OZ O2; cluster F-value$_{max}$ = 39465.97, p_{corr} = .03, time window = 836 - 1400 ms) and a positive fronto-centro-parietal cluster in the group with dysphoria (electrodes = FP1 FPZ FP2 F7 FZ F4 F8 FC5 FC1 FC2 FC6 C3 CZ C4 CP5 CP1 CP2 CP6 P7 P3; cluster F-value$_{max}$ = 41826.52, p_{corr} = .03, time window = -60 - 666 ms) and a significant as shown in Figure 3.9 and 3.10, respectively. The group with dysphoria showed increased theta power in response to unpleasant than neutral and pleasant stimuli (all $ps \leq .022$). Differently, the group without dysphoria revealed reduced theta power in response to unpleasant than neutral and pleasant stimuli (all $ps \leq .016$).

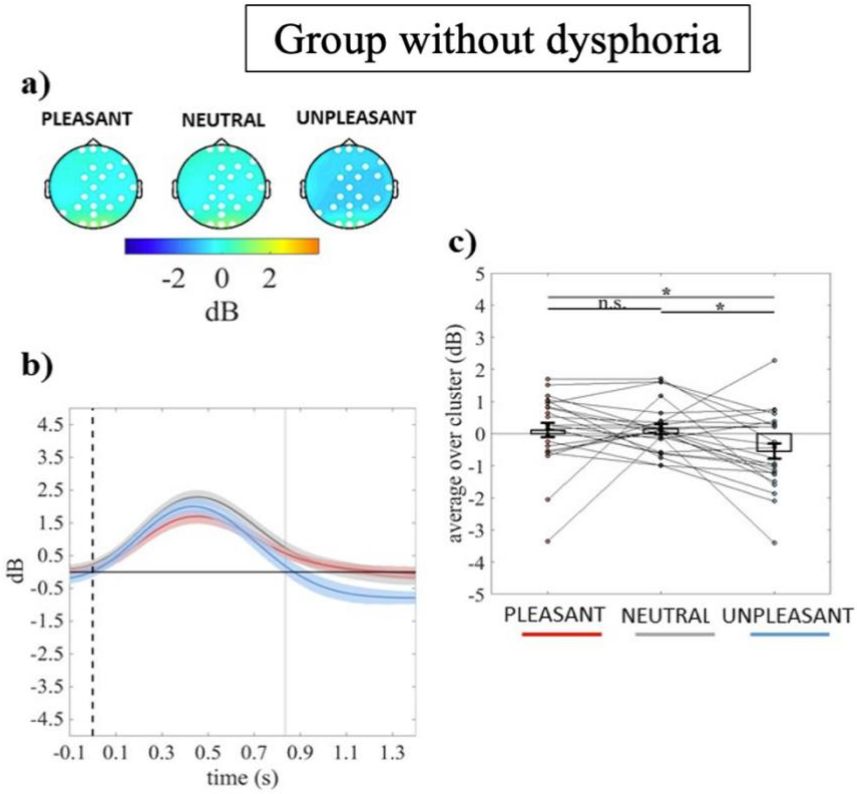

Figure 3.9 (Panel a) Topography of the mean event-related theta power [dB] of individuals without dysphoria averaged over the significant time points [836 - 1400 ms time window] for pleasant, neutral, and unpleasant conditions. (Panel b) Time course of grand-average event-related theta power of individuals without dysphoria averaged over the significant electrodes for pleasant [red line], neutral [grey line], and unpleasant [light blue line] conditions. Shaded areas represent ± SEM and the gray line represents the beginning of the significant time window [836 ms]. (Panel c) Mean event-related theta power of each participant [in the group without dysphoria] averaged over the significant electrodes and time points for pleasant, neutral, and unpleasant conditions. Each circle represents one participant; colored frames represent the mean event-related theta power across all participants and the solid black lines represent ± SEM. *$p < .05$.

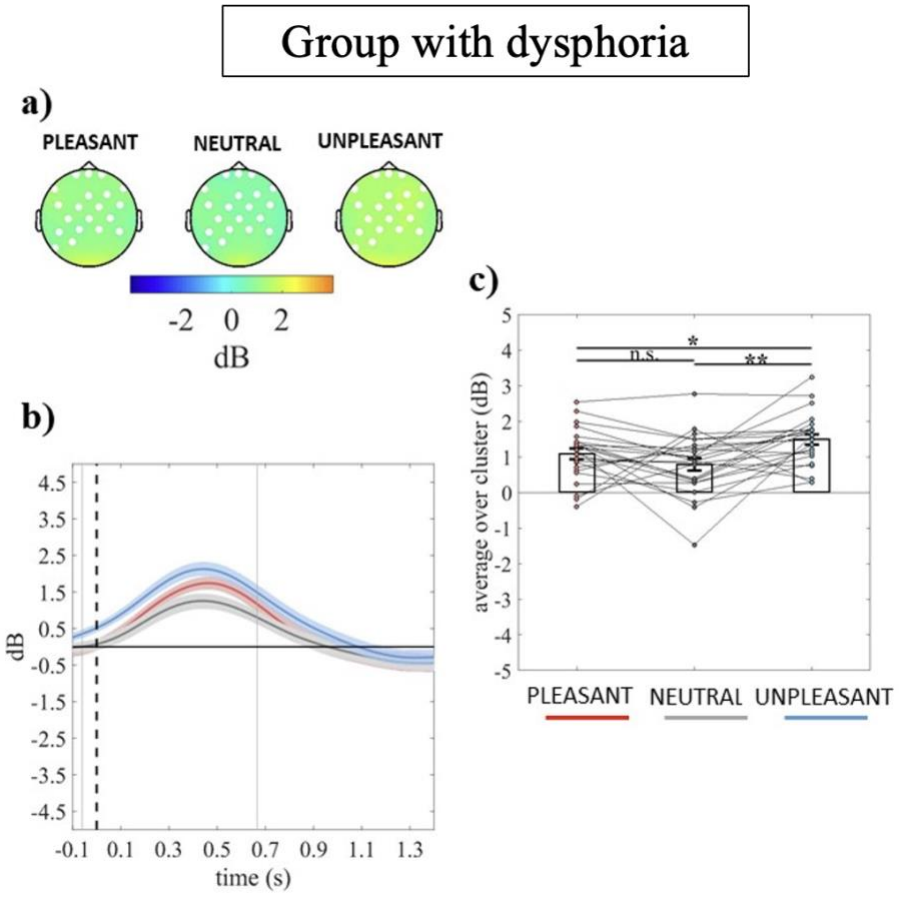

Figure 3.10 (Panel a) Topography of the mean event-related theta power [dB] of individuals with dysphoria averaged over the significant time points [-60 - 666 ms time window] for pleasant, neutral, and unpleasant conditions. (Panel b) Time course of grand-average event-related theta power of individuals with dysphoria averaged over the significant electrodes for pleasant [red line], neutral [grey line], and unpleasant [light blue line] conditions. Shaded areas represent ± SEM and gray lines represent the significant time window [-60 - 666 ms]. (Panel c) Mean event-related theta power of each participant [in the group with dysphoria] averaged over the significant electrodes and time points for pleasant, neutral, and unpleasant conditions. Each circle represents one participant; colored frames represent the mean event-related theta power across all participants and the solid black lines represent ± SEM. *p < .05; **p < .01.

Differences between groups in event-related theta power for each emotional category.

Unpaired *t*-test conducted on event-related theta power did not reveal any significant cluster for the difference between the groups within each emotional condition (all *p*s ≥ .125).

Alpha power

Differences among emotional categories in event-related alpha power. The cluster-based analyses on event-related alpha power did not reveal any statistically significant cluster in testing possible within-group differences (all *p*s ≥ .088).

Differences between groups in event-related alpha power for each emotional category. Unpaired t-test conducted on event-related alpha power did not reveal any significant cluster for the difference between the groups within each emotional condition (no cluster was detected; hence *p*-values were not generated).

3.5 Discussion

The present study examined affective disposition and cognitive processing in dysphoria through the analysis of the LPP and time-frequency changes within delta, theta, and alpha bands during the exposure to emotional pictures. Regarding affective disposition, the dysphoria group was expected to show a hypoactivation of the approach-related motivational system and, as suggested by the ECI model, a hypoactivation of the withdrawal-related motivational system. Second, the dysphoria group was expected to show selective facilitated top-down processing of unpleasant and a reduced processing of pleasant stimuli.

With respect to **affective disposition**, a pattern of increased event-related LPP and delta in response to all affective relative to neutral pictures emerged within both groups, indicating an affective modulation regardless of valence. Moreover, in line with the hypothesis, individuals with dysphoria showed a reduction of the LPP and delta to pleasant pictures relative to the group without dysphoria. This finding possibly indicates a reduced emotional responding to pleasant images and a hypoactivation of the approach-related motivational system in individuals with dysphoria. Indeed, delta oscillations are linked to motivational processing, whereby an increase in its power indicates the identification of potentially rewarding cues (e.g.,

Balconi & Mazza, 2009; Karakaş, 2020; Knyazev et al., 2009; Knyazev, 2011). Hence, reduced delta to pleasant images could denote reduced emotional responding to pleasant/rewarding stimuli in dysphoria. Additionally, the dysphoria group showed reduced LPP and delta to neutral pictures than the group without dysphoria, a pattern probably due to participants' motivational inertia, characteristic of depressive symptoms. Namely, it is plausible that the decreased motivation in dysphoria extended to non-relevant stimuli that did not elicit a saliency-detection process as prominent as in controls. Taken together, these findings provide support for the positive attenuation hypothesis in dysphoria. Conversely, the present findings are at odds with the negative potentiation hypothesis as well as with the reduced reactivity to unpleasant stimuli (Bylsma et al., 2008). However, blunted reactivity to unpleasant stimuli might specifically be a manifestation of clinical depression.

Furthermore, no significant difference between the dysphoria and the control group was found in the event-related alpha. This null finding may be due to different methodological approaches employed across studies. For instance, the present study differs in several methodological features from the few previous studies that employed a time-frequency approach (Messerotti Benvenuti et al., 2019; Stewart et al., 2014). Particularly, compared to a previous study (Messerotti Benvenuti et al., 2019), here an even more rigorous statistical approach was employed, whereby group level analyses were conducted on distinct time windows identified through cluster-based analysis conducted within each group separately. Although reduced alpha desynchronization to pleasant stimuli was reported in depression, results are still inconsistent in the literature (for a review see Van Der Vinne et al., 2017).

Regarding **affective cognitive processing**, the two groups showed distinct patterns of theta power changes at the within-subjects level. Of note, these within-subjects differences occurred at distinct time windows, indicating potentially different processes occurring within the same stage of stimulus analysis. In the literature, two stages of emotional processing of

theta power were identified: an early increase (~ 300 ms) related to automatic orienting and a later (after 300 ms) increase related to fine-grained top-down processing of salient stimuli (Knyazev, 2011; Zhang et al., 2013). Regarding the differences within the dysphoria group, an early increased in theta power for unpleasant pictures lasted until a later processing stage. On the other hand, within the control group, reduced theta for unpleasant pictures was evident only during a subsequent processing stage (836-1400 ms). It could be hypothesized that during the early stage of processing, individuals with dysphoria showed a preferential early orienting for unpleasant relative to both pleasant and neutral images. However, this effect was stable even after the early orienting stage, indicating that individuals with dysphoria performed a selective top-down processing towards unpleasant cues. Also, this pattern suggests that dysphoria may show a reduction in orienting towards pleasant pictures, which are processed as neutral ones. In contrast, controls showed a late reduction of top-down processing for unpleasant cues, suggestive for a conscious and adaptive regulation of these stimuli (Uusberg et al., 2014). Consistently, a previous study on healthy participants reported that a late (1000-4000 ms) theta activity decrease was associated with reappraisal, a regulation strategy aimed at modifying the meaning of an emotional situation. The late dampening of theta by reappraisal was interpreted as decreased prioritization of the stimuli by selective attention, following an initial evaluation of their affective saliency. Hence, the within-subjects pattern in dysphoria not only is consistent with a facilitated processing of unpleasant cues, but it might indicate a lack of adaptive regulation strategies as compared to controls. Since theta band has been largely associated with high-order cognitive processes (Ertl et al., 2013; Nigbur et al., 2011), in future studies it would be interesting to investigate event-related theta while participants engage in complex affective cognitive task.

From the current findings, the distinct role of delta and theta is supported. For instance, albeit speculative, not only do they represent distinct functional correlates of affective

processing, but they seem to be distinctively associated with the elaboration of pleasant and unpleasant content, respectively. In this regard, previous time-frequency studies on reward and loss processing have linked increased delta to reward sensitivity and increased theta to loss processing, describing them as two dissociable processes (e.g., Bernat et al., 2011; Nelson et al., 2018). Interestingly, a previous study reported that depressive symptoms were prospectively predicted by diminished reward-related delta but not loss-related theta (Nelson et al., 2018). Despite these studies employed a different paradigm, the present findings support the perspective of a pleasantness-related delta band and unpleasantness-related theta band. The current findings on theta are novel and future studies are warranted to better disentangle its role in the top-down processing of affective stimuli in dysphoria.

The time-frequency approach applied in the present study offers several methodological advantages compared to standard ERPs. Indeed, this approach allowed the separation of two peculiar measures of affective elaboration reflecting distinct processes occurring simultaneously, namely affective disposition and top-down processing. Furthermore, in addition to the analysis of evoked oscillations, time-frequency analysis also incorporates induced oscillations, known to carry important information about cognitive processes (Herrmann et al., 2014).

In accordance with findings of previous studies on subclinical (e.g., Messerotti Benvenuti et al., 2019; Messerotti Benvenuti et al., 2015; Sloan & Sandt, 2010) and clinical depression (e.g., Dichter et al., 2004), self-report measures of valence and arousal did not differ between groups. Overall, this suggests that differences in electrocortical measures across groups cannot be attributed to differences in subjective ratings of valence and arousal. In addition, these findings would suggest that electrocortical measures of emotional responding may be more sensitive measures than subjective ratings to identify subclinical depressive symptoms. Indeed, these measures may reflect unaware attentional processes that are not

discernible with subjective reports of emotional experience. These results highlight the importance of employing psychophysiological measures in conjunction with self-report ones for a better understanding of abnormal patterns of affective processes in dysphoria.

Some limitations should be acknowledged. First, considering that the present study was based on a community sample and that dysphoria is more prevalent among the female population (Rodríguez et al., 2021), most of the participants within the dysphoria group belonged to the female sex. This sex unbalance might not allow the generalization of the findings to the male population and future studies are warranted to replicate the findings and increase their generalizability. Furthermore, although the emotional passive viewing task is a valid and widely used paradigm to study affective processing (e.g., Codispoti et al., 2006; Klawohn et al., 2020), future studies that include specific experimental manipulations during the exposure to emotional stimuli are warranted to clarify the functional correlates of delta, theta and alpha frequency bands in affective tasks.

In conclusion, the present study granted novel evidence on distinct but interrelated facets of affective elaboration in dysphoria, mainly characterized by a hypoactivation of the approach-related motivational system and a sustained facilitated cognitive processing along with reduced adaptive regulation of unpleasant stimuli. In terms of RDoC dimensions, these results suggest a reduced functioning of the Positive Valence Systems as well as a potential interaction between the Negative Valence Systems and the Cognitive Systems in conferring depression risk. Considering that dysphoria is a condition known to considerably increase the risk of depression, these patterns of affective processing may represent quantitative measures allowing for early identification and treatment of depressed mood.

3.6 Study 1b: Reduced electrocortical responses to appetitive stimuli are driven by anhedonia in dysphoria

3.6.1 Introduction

The goal of these additional analyses was to better understand the association and pathways that lead to a reduced LPP and delta time-frequency power to pleasant stimuli in individuals with dysphoria. Considering that the reduction in these measures observed in dysphoria was interpreted as a hypoactivation of the Positive Valence Systems of approach motivation, it could be hypothesized that symptoms of anhedonia drive the reduced neural responses to pleasant cues in this group. Particularly, anhedonia is defined as a lack of interest or pleasure in normally enjoyable experiences and is conceptualized as arising from a hypoactivation of the motivational approach system (Davidson, 1998; Pizzagalli, 2008; Klawohn et al., 2021).

To better understand the direct and mediated paths leading from dysphoria to reduced LPP and delta power to pleasant stimuli, path analysis models were performed. Specifically, it was hypothesized that the association between reduced neural responses to pleasant cues (LPP and delta power) and dysphoria was mediated by symptoms of anhedonia.

3.6.2 Methods

To have a single measure of LPP and delta to pleasant cues, residualized difference measures for the LPP and delta power were determined by saving the unstandardized residuals in linear regressions predicting LPP to pleasant images from LPP to neutral images (i.e., LPP_{resid}) and predicting delta power to pleasant images from delta power to neutral images (i.e., $Delta_{resid}$), respectively. First, Pearson correlations were conducted between the two measures, the anhedonia subscale of the BDI (items 4, 12, 22 were summed to form an index of anhedonic

symptoms; Joiner et al., 2003), and non-anhedonia BDI scores (The remaining 18 BDI items were summed, to form a measure of non-anhedonic depressive symptoms; Joiner et al., 2003).

Then, path analyses were conducted to assess whether the relation between each EEG measure that was significantly different between the two groups and dysphoria status was mediated by anhedonia. Path analyses are extensions of regression models and require the specification of a causal ordering of the variables. Assuming that the defined structure is robust, these models give a cleaner and more detailed picture of the significant effects. The pattern of associations was examined using R package Lavaan (R Core Team, 2015; Rosseel, 2012), with combinations of observed scores (i.e., centered mean score) that composed the latent variable of anhedonia (BDI items 4, 12, 21) and observed variables (EEG measures and group status). Path coefficients were estimated using the maximum likelihood method. The possible causal associations (direct, indirect, and total effects) between LPP or delta power, dysphoria status, and anhedonia were tested. A bootstrap procedure was used (with 1000 replications) to generate empirical sampling distribution of effects, which provided confidence intervals for the direct, indirect, and total effects. Indirect effects were considered significant when confidence intervals did not include zero (Preacher & Hayes, 2008). Model fit was assessed by examining the comparative fit index (CFI; Marsh & Hau, 2007) and the root mean square error of approximation (RMSEA; Cole & Maxwell, 2003). Values > 0.95 are desirable for the CFI, while RMSEA values should be ≤ 0.05 for a good model fit (Hu & Bentler, 1999).

3.6.3 Results

Correlations are shown in Table 3.1. The LPP_{resid} did not significantly correlate with $Delta_{resid}$ and the other measures. $Delta_{resid}$ was negatively correlated with anhedonia but not with BDI scores.

Table 3.1 Pearson correlations of LPP and delta power to pleasant cues, anhedonia and BDI global scores.

	LPP_{resid}	$Delta_{resid}$	Anhedonia
$Delta_{resid}$	.13	-	
Anhedonia	-.11	-.30*	-
Non-anhedonic BDI scores	-.14	-.20	.79**

Note. LPP = late positive potential. *p <.05. **p < .01.

The path model on the LPP fit the data well (CFI = 1.00; RMSEA = 0.00) but no direct effect of the LPP_{resid} (β= -.004, SE=.016, p = 0.82, 95% CI [-0.036 0.026]) on group status or indirect effect of the LPP_{resid} through anhedonia (β= -.018, SE=.017, p = 0.29, 95% CI [-0.047 0.023]) emerged.

The path model on $Delta_{resid}$ fit well the data (CFI = 1.00; RMSEA = 0.00) and showed no direct effect of $Delta_{resid}$ (β= -.10, SE=.100, p = 0.34, 95% CI [-0.269 0.135]) but significant indirect (β= -.22, SE=.101, p = 0.03, 95% CI [-0.436 -0.033]) and total effects (β= -.31, SE=.105, p = 0.003, 95% CI [-0.504 -0.065]) through anhedonia (Figure 3.11)[3].

[3] As a control analysis, the same path model was run by including the non-anhedonic BDI scores instead of anhedonia scores and the indirect path between delta and group through non-anhedonic BDI scores was not significant (p = 0.910 CI 95% [-0.428 0.649]).

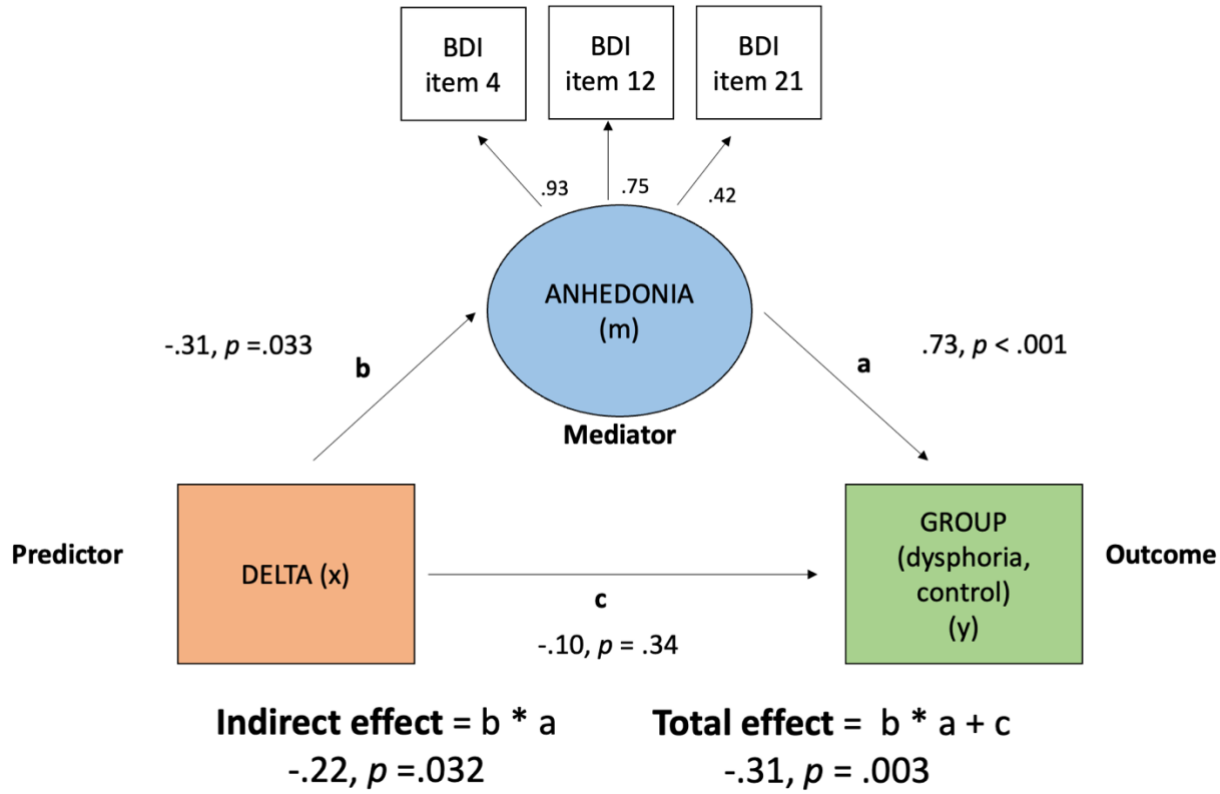

Figure 3.11 Path diagram depicting direct and indirect associations between $Delta_{resid}$ and Group with $Delta_{resid}$ as the predictor, Anhedonia as the mediator, and Group as the outcome. Standardized path coefficients and *p*-values are shown for each association. Anhedonia is a latent variable defined by BDI items 4, 12, and 21 (observed variables).

3.6.4 Discussion

These additional analyses aimed at examining whether anhedonia, a dimension thought to underlie reactivity towards pleasant cues, was a significant mediator of the association between neural responses (LPP and delta power) to pleasant images and group status (dysphoria, controls).

Partly in line with the hypotheses, the association between time-frequency delta power, but not LPP, and group status was significantly mediated by anhedonia scores. Namely, a causal pathway can be inferred, whereby anhedonia was responsible for the observed reduced delta power to pleasant cues in individuals with dysphoria. Notably, the same did not emerge when considering non-anhedonic scores of the BDI-II scale, indicating a selective role of anhedonia in driving blunted delta power to appetitive cues in dysphoria. These results further support the

hypothesis that delta activity reflects the activation of approach motivation. Of note, LPP and time-frequency delta power to pleasant pictures were not significantly correlated, suggesting that frequency-based representation provides unique information that is not apparent with time-domain analysis. Overall, it could be hypothesized that these two measures could represent distinct aspects of positive emotional reactivity and that delta power is mostly driven by anhedonia.

CHAPTER IV

STUDY 2: REDUCED ELECTROCORTICAL RESPONSES TO PLEASANT PICTURES IN CLINICAL DEPRESSION: A TIME-DOMAIN AND TIME-FREQUENCY DELTA INVESTIGATION[4]

4.1 Abstract

Study 1 demonstrated that individuals with subclinical levels of depression are characterized by reduced approach-related motivation, included within the Positive Valence System dimension of the RDoC and assessed with the LPP and time-frequency delta power to pleasant images. Additionally, Study 1 showed that the reduced delta power to appetitive cues in dysphoria was mediated by anhedonia, supporting the link between this neural measure and the PVS.

The objective of Study 2 was to extend the findings from Study 1 to a group of **clinically depressed individuals**. Particularly, the present study aimed at analyzing time-frequency delta in depression and at investigating whether the combination of time-domain (LPP) and time-frequency data would explain additional variance in the depression status. EEG was recorded during a passive viewing task of pleasant and neutral pictures in a community-based sample of 75 adults with a current depressive disorder and 42 controls. The LPP of this sample was previously computed and reported, and participants with depression showed reduced LPP to pleasant images relative to controls. A time-frequency analysis on event-related changes within delta frequency band was conducted. Cluster-based statistics revealed a centro-parietal increase in delta power to pleasant relative to neutral pictures in the control group but

[4] Results from this study have been published in **Dell'Acqua, C.,** Brush, C. J., Burani, K., Santopetro, N. J., Klawohn, J., Messerotti Benvenuti, S., & Hajcak, G. (2022). Reduced electrocortical responses to pleasant pictures in depression: A brief report on time-domain and time-frequency delta analyses. *Biological Psychology,* 170, 108302.

not within the depression group. Moreover, a fronto-centro-parietal reduction in delta power to pleasant pictures emerged in depression relative to controls. Both a smaller LPP and delta power to pleasant pictures were independently related to depression status. The model explained a greater amount of variance (Nagelkerke R^2 = .11) compared to the logistic regression where the LPP_{res} was entered as independent predictor of group status (Nagelkerke R^2 = .07).

These data suggest that delta power might be a promising electrocortical correlate of the hypoactivation of the approach-related motivational system in clinical depression. Additionally, a blunted delta and LPP might reflect unique processes related to clinical depression. A combination of these measures can be leveraged together to enhance clinical utility.

4.2 Introduction

The hypoactivation of the approach-related motivational system in depression (Admon & Pizzagalli, 2015) has been extensively documented by event-related potentials (ERPs) studies, that reported a blunted late positive potential (LPP) to pleasant pictures in current depression (Klawohn et al., 2021; Weinberg et al., 2016; for a review see Hajck Proudfit et al., 2015).

As detailed in previous Chapters, additional insight into emotional reactivity can be provided using time-frequency decomposition of electroencephalography (EEG) data (e.g., Bernat, Nelson, & Baskin-Sommers, 2015; Herrmann et al., 2014). Time-frequency approach allows disentangling multiple overlapping spectral components that are embedded in the time-domain data (Foti et al., 2015). Conceptualizing EEG data as a multidimensional time-frequency signal has advantages over ERP analyses (Cohen, 2014). For example, task-related information, such as non-phase locked (i.e., induced) dynamics, can be lost during ERP

averaging but are observable with time-frequency analysis, which adopts a trial-by-trial approach (Cohen, 2014; Herrmann et al., 2014).

Delta oscillations (< 3 Hz) are associated with the motivational processing of salient stimuli (Bernat et al., 2015; Foti et al., 2015; Güntekin & Başar, 2016; Nelson et al., 2018; Knyazev, Slobodskoj-Plusnin, & Bocharov, 2009; Knyazev, 2012; Williams et al., 2021; Zhang et al., 2013). Considering that delta power might add additional information to time-domain measures in the study of emotional reactivity in depression, it stands to reason that both time-domain and time-frequency might be leveraged together to better understand depression.

In the previous Chapter, a smaller centro-parietal delta power to pleasant images in individuals with dysphoria was observed. Time-frequency delta activity to emotional pictures, however, has not been examined in individuals with a clinical diagnosis of depressive disorder. Also, whether delta power represents a unique indicator of depression status, independent of the time-domain LPP, remains unexplored.

In the current study, emotional reactivity to pleasant vs. neutral images through the analysis of time-frequency changes during an emotional passive viewing task of pleasant and neutral pictures in individuals with and without clinical depression was examined. The depression group was expected to show a blunted delta activity in response to pleasant pictures relative to healthy controls. A second goal of this work was to examine whether utilizing a combination of LPP and delta activity would explain additional variance in depression status. In addition, the association of both LPP and delta power with self-report measures of interest (i.e., depressive symptom severity and anhedonia) was investigated.

4.3 Method

Participants

The present study is a secondary analysis of EEG data collected during a passive viewing paradigm (Klawohn et al., 2021). The present study included 117 (92 F) participants between 18 and 60 years of age. The depressed (DEP) group included 75 (58 F, 17 M) participants that met diagnostic criteria for a current depressive disorder (current MDD and/or persistent depressive disorder, PDD), and scored equal to or greater than 13 on the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). The healthy control group (HC) included 42 (34 F, 8 M) participants that never met the diagnostic criteria for a mood disorder, did not currently meet criteria for any psychiatric disorder, and scored less than a 13 on the BDI-II. Exclusion criteria included the presence of a lifetime diagnosis of a bipolar or psychotic disorder or any neurological disorders, a current substance use disorder.

The sample included both right- and left-handed participants, as assessed with the Edinburgh handedness inventory (Oldfield, 1971). The two groups did not differ in terms of handedness ($p = 0.232$). Participants were compensated for their participation ($20 per hour). All procedures were approved by the local ethics committee.

Clinical interviews

The presence of current and past mood disorders was determined using the Structured Clinical Interview for DSM-5 (SCID-5-Research Version; First et al., 2015). Other past and present psychopathology was evaluated using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998), updated for DSM-5 (version 7.0.2) (Sheehan et al., 1997).

Self-report symptoms

Depressive symptoms in the past two weeks were assessed using the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). Higher scores indicate greater depressive symptoms. Internal consistency resulted high for the 21 items of the BDI-II (Cronbach's α = .96). As in the additional analyses to Study 1 (Chapter III), anhedonia and non-anhedonic depressive symptoms were also computed based on BDI items (anhedonia: 4, 12, 21; non-anhedonic: all the other 18 items).

Participants also completed the anhedonia facet subscale of the Personality Inventory for DSM-5 (PID-5; Krueger et al., 2012). Higher scores indicate greater anhedonia. Internal consistency resulted high for the items of the PID-5 anhedonia subscale (Cronbach's α = .95).

EEG recording

The electroencephalogram (EEG) was recorded using a 32-channel system (ActiCHamp, Brain Products GmbH) referenced online to Cz with a sampling rate of 1000 Hz using a bandpass recording filter of 0.01–100 Hz. Both vertical and horizontal electrooculograms (EOGs) were recorded using a bipolar montage to monitor eye movements and eye-blinks.

Experimental task and procedure

The picture viewing task comprised 60 color pictures selected from the International Affective Picture System (IAPS; Lang, Bradley, Cuthbert, 2008); 30 pleasant images (e.g., erotic and affiliative images) and 30 neutral images (e.g., objects, humans with neutral facial expression; specific IAPS picture numbers and normative ratings are listed in the supplementary material).

All pictures were presented for 1500 ms, spanning approximately 15 by 20 degrees of visual angle, in random order across three blocks of 20 trials. Each picture was preceded by a fixation cross with a random duration of 500–900 ms. Participants were required keep their gaze on the center of the screen. Picture presentation was followed by a variable intertrial interval of 500-900 ms, during which a white fixation cross was presented.

EEG Data Processing

Time domain

Offline time-domain EEG data processing was conducted using Brain Vision Analyzer (Brain Products, Gilching, Germany). Data was referenced to the average mastoid electrodes and filtered from 0.01 to 30 Hz. Epochs from 200 ms before until 1200 ms after picture onset were extracted and corrected for eye movement artifacts (Gratton, Cole, & Donchin, 1983). Segments containing voltage steps >50 mV between sample points, a voltage difference of 175mV within a 400 ms interval, or a maximum voltage difference of <0.5mV within 100 ms intervals were automatically rejected and additional artifacts were identified and removed based on visual inspection. Baseline correction was applied using the 200 ms pre-stimulus interval. Stimulus-locked averages were calculated separately for pleasant and neutral images, and the LPP was quantified at a parietal electrode-pool (Pz, Cz, CP1 and CP2) as the mean amplitude from 400 to 1000 ms after picture onset.

Time-Frequency domain

The processing pipeline for the time-frequency domain was similar to the one conducted for the time domain. Here, the extracted time windows were wider to allow for the discarding of edge effects, and the artifact rejection procedure was somewhat more conservative. EEG data processing was conducted in Brainstorm (Tadel et al., 2011). The

signal was filtered offline with a band-pass filter of 0.3-30 Hz to minimize slow drifts that could have adverse effects on time-frequency decomposition. Also, independent component analysis (ICA) was used to correct for blink artifacts. The data were segmented into epochs from 500 ms before until 1500 ms after picture onset.

Time-frequency analysis was conducted using Morlet wavelet transformation on individual trials for each 1-Hz frequency bin between 1 and 30 Hz, using a mother wavelet at 1 Hz with 3-s time resolution (as calculated by the full width at half maximum, FWHM). Time-frequency decompositions were then averaged for each participant and emotional condition, and the event-related spectral perturbation (ERSP) was computed as the change in power expressed in decibels (dB) relative to the baseline (−300 to −100 ms) in each frequency bin at each time point. Then, data were grand averaged across each group for each emotional condition.

With respect to time-frequency data, a cluster-based permutation approach was run on the event-related delta (1–3 Hz), as implemented by the FieldTrip toolbox (Oostenveld et al., 2011). With this approach, the theoretical underlying distribution of test statistics under the null hypothesis is generated by the data itself, by iteratively shuffling the condition labels over trials or over subjects and recomputing the statistics. If the test statistic associated with the non-shuffled data falls within the distribution of the null-hypothesis test statistic values, the null hypothesis cannot be rejected and this would indicate that the observed data could have been randomly generated (Cohen, 2014; Luck, 2014b). With cluster-based correction, at each iteration of the null-hypothesis distribution generation, the outcome is units of clusters instead of single pixels (i.e., electrodes) (Cohen, 2014). In the present study, the differences within emotional conditions or between groups were shuffled pseudo-randomly 2000 times. To obtain a ‘null’ distribution of effect sizes, the maximal cluster-level statistics (i.e., the sum of values across contiguously significant electrodes and time points at the threshold level) were extracted

for each shuffle. For each significant cluster in the (non-shuffled) data, the cluster-corrected *p*-value was computed as the statistics of the proportion of clusters in the null distribution that exceeded the one obtained for the cluster in question. Clusters with a $p_{corr} < .05$ were considered statistically significant. This approach provides solid control over type I error rate arising from multiple comparisons across electrodes and time points (Maris & Oostenveld, 2007). Cluster-based repeated measures ANOVAs were conducted to test within-group differences in event-related power changes between emotional categories (i.e., pleasant versus neutral). Two-tailed independent samples *t*-tests were conducted to test between-group (i.e., DEP versus HC) differences within each emotional category.

Further statistical analyses were conducted using a two-tailed $\alpha = .05$. Delta power was extracted according to the significant time window and location (i.e., sensors) that emerged from the cluster-based between-group differences for pleasant pictures. Residualized difference measures for the LPP and delta power were determined by saving the unstandardized residuals in linear regressions predicting LPP to pleasant images from LPP to neutral images (i.e., LPP_{resid}) and predicting delta power to pleasant images from delta power to neutral images (i.e., $Delta_{resid}$), respectively. The Shapiro-Wilk test was conducted to ensure that data was normally distributed. Then, within each group, Pearson correlations were performed. Finally, a logistic regression was conducted to examine whether the $Delta_{resid}$ and LPP_{resid} explained unique or shared variance in depression diagnostic status, and to determine the amount of variance that was explained by using the two measures as simultaneous predictors of depression status.

4.4 Results

Characteristics of the sample

Table 4.1 illustrates demographic and clinical characteristics of the sample (DEP, HC). In the DEP group, several individuals met diagnostic criteria for one or more comorbid psychiatric diagnoses, in particular: panic disorder (*n* = 13), agoraphobia (*n* = 8), social anxiety disorder (*n* = 12), obsessive compulsive disorder (*n* = 5), post-traumatic stress disorder (*n* = 4), generalized anxiety disorder (*n* = 19), specific phobia (*n* = 4), eating disorder (*n* = 7), somatic symptoms disorder (*n* = 3) and illness anxiety (*n* = 2). Moreover, in the DEP group, 39 individuals (52 %) were currently taking psychotropic medication (antidepressants, *n* = 33; anxiolytics, *n* = 13; stimulants, *n* = 5; anticonvulsants, *n* = 5).

Table 4.1. Demographic, clinical variables, and EEG data for group with a current depressive disorder (DEP) and the healthy control group (HC).

	HC group (*n* = 42)	**DEP group** (*n* = 75)	*p*
Age	37.0 (14.2)	39.70 (11.9)	.280
Sex (% female)	77.33	80.95	.847
Ethnicity (% Caucasian)	92.86	92.00	.571
Education	16.50 (1.60)	16.00 (15.00)	.229
BDI	2.21 (3.06)	29.40 (9.32)	< .001
PID 5-Anhedonia	2.48 (3.40)	13.80 (5.58)	< .001
LPP pleasant (μV)	6.06 (4.19)	4.02 (4.31)	.020
LPP neutral (μV)	-2.62 (3.54)	-3.05 (3.48)	.520
Delta pleasant (dB)	0.99 (0.37)	0.84 (0.33)	.030
Delta neutral (dB)	0.89 (0.25)	0.85 (0.38)	.610

BDI-II, Beck Depression Inventory-II; LPP, late positive potential; μV, microvolts; dB, decibels. *Note*: Means are displayed, standard deviations are in parentheses.

Cluster-based analysis on Delta power

Differences among emotional categories in event-related delta power. The cluster-based analysis on event-related delta power showed a significant positive centro-parietal cluster (electrodes = CP1, PZ, P3, CP2) in the HC group (cluster *F*-valuemax = 9908.62, p_{corr} = .036, time window -0.010 to 0.594 s; Cohen's *d* = 0.44), with significantly larger delta power to pleasant relative to neutral pictures (Figure 4.1, panel a and b). A marginally significant cluster emerged in event-related delta power by emotional category within the DEP group, (electrodes = PZ, P4, CP2; cluster *F*-valuemax =4810.42, p_{corr} = .052, time window 0.784 to 1.228 s; Cohen's *d* = 0.06), showing a decrease of delta power to pleasant relative to neutral in a late time window (Figure 4.1, panel c and d).

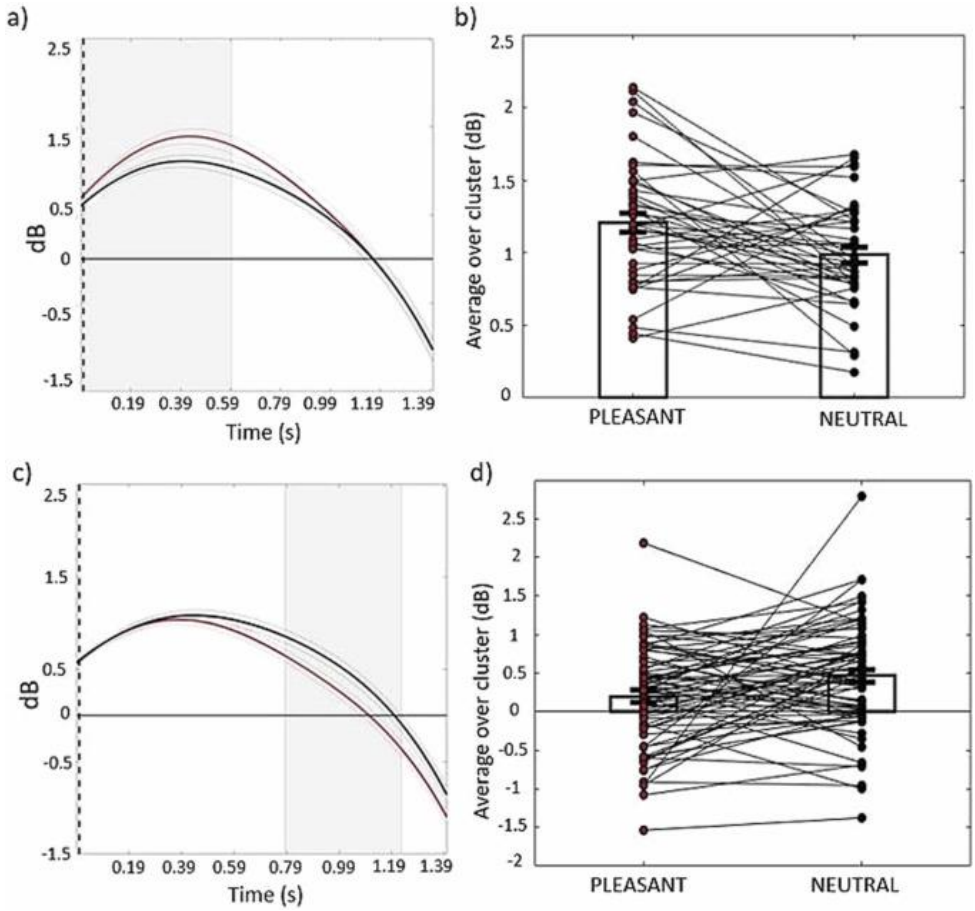

Figure 4.1 (Panel a) Time course of grand-average event-related delta power of control individuals averaged over the significant electrodes for pleasant (red line) and neutral (black line) conditions. Shaded areas represent ± standard error of the mean (SEM) and the gray box represents the end of the significant time window (0.594 s). (Panel b) Mean event-related delta power of each participant (in the control group) averaged over the significant electrodes and time points for pleasant and neutral conditions. Each circle represents one participant (Panel c) Time course of grand-average event-related delta power of individuals with depression averaged over the marginally significant electrodes for pleasant (red line) and neutral (black line) conditions. Shaded areas represent ± standard error of the mean (SEM) and the gray box represents the significant time window. (Panel d) Mean event-related delta power of each participant (in the depression group) averaged over the significant electrodes and time points for pleasant and neutral conditions. Each circle represents one participant.

Differences between groups in event-related delta power for each emotional category.

Cluster-based independent samples *t*-tests on event-related delta power revealed a significant positive cluster for the difference between the two groups for pleasant pictures (electrodes = FZ, FCZ, FC1, C3, CP5, CP1, PZ, P3, P7, O1, P4, CP2; cluster *t*-valuemax = 9879.36; p_{corr} = .030, time window = -0.010 to 0.860 s; Cohen's $d = 0.42$), with reduced delta power to pleasant pictures in the DEP compared to HC group (Figure 4.2, panel a, b and c). There were no group differences in delta power to neutral pictures.

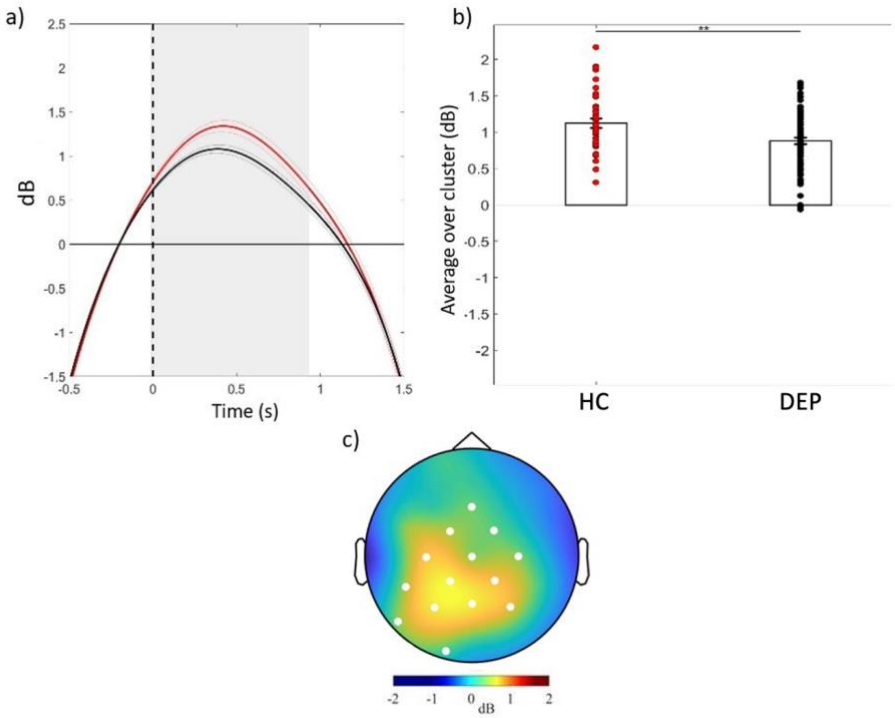

Figure 4.2 (Panel a) Time course of grand-average event-related delta power averaged over the significant electrodes for the pleasant condition in the depression (DEP) group (black line) and the control (HC) group (red line). Shaded areas represent ± standard error of the mean (SEM); the gray box represents the significant time window. (Panel b) Mean event-related delta power of each participant in the DEP group and the HC group averaged over the significant electrodes and time points for the pleasant condition. Each circle represents one participant. (Panel c) Topography of the mean difference between groups in event-related delta power (dB; DEP group minus HC group) averaged over the significant time points (-0.010 to 0.860 s time window) for the pleasant condition. $^{**}p < .01$.

Correlations

The LPP_{resid} and $Delta_{resid}$ were uncorrelated across the whole sample (r (115) = .07, p = .437) and within each group separately (DEP: r (73) = -.03, p = 0.801; HC: r (39) = .13; p = .419), suggesting that these two measures reflect distinct processing of positive emotional reactivity. Within the DEP group, contrarily to what emerged in Study 1, the correlation between LPP_{resid} and self-report anhedonia approached significance (r (73) = -.212, p = .067), whereas there was no correlation between other variables (all ps >.229). In the HC group, there were no correlations among study variables (all ps >.316).

Logistic regression

Results of the logistic regression are shown in Table 4.2. The multiple logistic regression showed that both smaller LPP_{resid} and smaller $Delta_{resid}$ were independently related to increased likelihood of being diagnosed with a depressive disorder[5]. The model explained a greater amount of variance (Nagelkerke R^2 =0.11) compared to the logistic regression where the LPP_{res} was entered as independent predictor of group status (Nagelkerke R^2 =0.07).

Table 4.2. Results of the logistic regression analysis predicting diagnostic status (DEP, HC) from LPP and Delta power.

Measure	Prediction of diagnostic status (DEP, HC)				
	R^2	$\chi 2$	OR	95% CI_{OR}	*p*
Model on combined LPP and delta power	0.11	10.1			
LPP_{resid}			0.89	0.80 – 0.98	.023
$Delta_{resid}$			0.29	0.08 – 0.99	.050

Note. Logistic regression was used to predict the dichotomous dependent variable diagnosis of depression (0 = absent, 1 = present); The Nagelkerke R^2 and $\chi 2$ statistics are reported for the logistic regression models. CI = confidence intervals; OR = odds ratio.

4.5 Discussion

The current study sought to extend the findings detailed in Chapter III on dysphoria by examining emotional reactivity to pleasant pictures in adults with a current clinical depressive disorder by examining time-frequency changes within the delta frequency band in response to pleasant and neutral pictures (Lang et al., 2008). Consistent with the hypotheses, individuals

[5] Considering that, due to the different EEG data processing method required in the time-frequency analysis, the current sample was slightly different from the one included in the previous work (Klawohn et al., 2021), a logistic regression with the LPP_{resid} entered as an independent predictor of group status was run. The results confirmed a significant model wherein LPP_{resid} predicted depression status (Nagelkerke R^2 =0.07, $\chi 2$ = 5.97; Odds ratio = 0.88, p = .018).

with depression were characterized by reduced delta power to pleasant pictures, but not neutral, relative to healthy controls.

With respect to the time-frequency analysis, the control group showed increased event-related delta power to pleasant relative to neutral images, indicating that affective modulation of pleasant images occurred. However, within the depression group, a significant difference between the two conditions did not emerge, indicating the **absence of affective modulation** in this sample. Moreover, a marginally significant difference between the two conditions emerged within the depression group, whereby delta power was reduced to pleasant relative to neutral pictures in a late time window.

Furthermore, as expected, the depression group showed reduced event-related delta power to pleasant images relative to the control group. This is consistent with findings from Chapter III on dysphoria. Overall, these findings provide support for the view of depression as characterized by a **hypoactivation of the approach-related motivational system** in the brain. Considering this result in addition to the absence of within-group affective modulation, the present study suggests that there might be a continuum of reduced approach motivation and RDoC Positive Valence System functioning based on the severity of depressive symptoms, with clinically significant depression related to a more extended reduction in approach motivation relative to subclinical conditions. However, contrary to the previous study, delta power to appetitive pictures was not inversely correlated with anhedonia scores.

Nevertheless, the combination of delta power and LPP to pleasant pictures increased the explained variance in the likelihood of suffering from depression relative to the sole employment of either time-domain or frequency-based measures. This study was the first attempt to simultaneously examine both EEG measures in clinical depression and it suggests that leveraging time-frequency delta in conjunction with time-domain measures might be particularly useful in better elucidating the pathophysiology of depression. The time domain

and spectral representations were not correlated, suggesting that frequency-based representation provide unique information that is not apparent with time-domain analysis. Considering that these electrocortical measures were uniquely related to depression status they might reflect distinct processes relevant to depression. In line with the fact that the LPP and delta power are separate predictors of depression status, these two measures were uncorrelated, suggesting that they could represent distinct aspects of positive emotional reactivity.

Considering the extensive literature indicating that LPP to pleasant stimuli is a reliable indicator of depression status (for a review see, Hajcak Proudfit et al., 2015), the present study suggests that the analysis of time-frequency delta could be a complementary measure in the prediction of depression. The analysis of both LPP and delta can reveal two interrelated processes, namely reduced motivated attention to positively valenced content and reduced approach-related motivation, respectively.

The present study has some limitations worth noting. First, most of the participants included in the study were female and Caucasian. Future investigations should replicate these findings in more diverse samples. Also, the objective of this study was to focus on approach motivation deficits in a clinical sample and unpleasant images were not employed. In the previous study detailed in Chapter III, we did not find between-group differences in any of the EEG measures but distinct within-group patterns for theta power. It would be interesting in the future to explore whether those findings extend to a clinical group and whether individuals with clinical depression are characterized by extended deficits in attending and processing unpleasant stimuli.

In conclusion, the current study provided converging evidence across multiple approaches that a blunted emotional reactivity to pleasant pictures, reflecting Positive Valence Systems functioning, is an indicator of clinical depression. Considering that both LPP and time-frequency delta power can be obtained from the same task, our findings suggest that a

combination of EEG measures can be leveraged together from the same paradigm to enhance clinical utility.

4.6 Study 2b: Reduced electrocortical responses to appetitive stimuli are not driven by anhedonia in clinical depression

4.6.1 Introduction

The goal of this section was to replicate the additional analyses of Study 1 (Chapter III) to better understand the association and pathways that lead to a reduced LPP and delta time-frequency power to pleasant stimuli in individuals with clinical depression. In brief, considering that the pattern of blunted electrocortical responses to pleasant stimuli was interpreted as a hypoactivation of the Positive Valence Systems of approach motivation in MDD, it was hypothesized that symptoms of anhedonia could drive the reduced neural responses to pleasant cues in this clinical group. Particularly, additional analyses of Study 1 revealed that the link between reduced delta power to pleasant images and dysphoria was mediated by anhedonia symptoms.

To better understand the direct and mediated paths leading from MDD to reduced LPP and delta power to pleasant stimuli, path analysis models were performed. Specifically, it was hypothesized that the association between reduced neural responses to pleasant cues (LPP and delta power) and MDD was mediated by symptoms of anhedonia.

4.6.2 Methods

First, Pearson correlations were conducted among the EEG measures ($Delta_{resid}$, LPP_{resid}) anhedonia subscale of the BDI (items 4, 12, 22 were summed to form an index of anhedonic symptoms; Joiner et al., 2003), non-anhedonia BDI scores (The remaining 18 BDI

items were summed, to form a measure of non-anhedonic depressive symptoms; Joiner et al., 2003) and the anhedonia subscale of the PID-5.

Then, similarly to Chapter III, path analyses were conducted to assess whether the relation between each EEG measure that was significantly different between the two groups and MDD status was mediated by the anhedonia. The pattern of associations was examined using R package Lavaan (R Core Team, 2015; Rosseel, 2012), with combinations of observed scores (i.e., centered mean score) that composed the latent variable of anhedonia (BDI items 4, 12, 21, Anhedonia PID-5 subscale) and observed variables (EEG measures and group status). Path coefficients were estimated using the maximum likelihood method. The possible causal associations (direct, indirect, and total effects) between LPP or delta power, MDD status, and anhedonia were tested. A bootstrap procedure was used (with 1000 replications) to generate empirical sampling distribution of effects, which provided confidence intervals for the direct, indirect, and total effects. Indirect effects were considered significant when confidence intervals did not include zero (Preacher & Hayes, 2008). Model fit was assessed by examining the comparative fit index (CFI; Marsh & Hau, 2007) and the root mean square error of approximation (RMSEA; Cole & Maxwell, 2003). Values > 0.95 are desirable for the CFI, while RMSEA values should be ≤ 0.05 for a good model fit (Hu & Bentler, 1999).

4.6.3 Results

Correlations are shown in Table 3.1. The LPP_{resid} did not significantly correlate with $Delta_{resid}$ and the other measures. $Delta_{resid}$ did not correlate with measures of anhedonia or non-anhedonic BDI scores.

Table 4.3 Pearson's correlations of LPP and delta power to pleasant cues, anhedonia, and BDI global scores.

	LPP_{resid}	$Delta_{resid}$	BDI Anhedonia	PID-5 Anhedonia
$Delta_{resid}$	.03	-		
BDI Anhedonia	-.10	-.06	-	
PID-5 Anhedonia	-.10	-.12	0.80^{**}	-
Non-anhedonic BDI scores	.01	-.14	$.90^{**}$	$.82^{**}$

Note. LPP = late positive potential. *p <.05. **p < .01.

The path model on the LPP fit the data well (CFI = 1.00; RMSEA = 0.00) but only a direct effect of the LPP_{resid} (β= .01, SE=.01, p = .043, 95% CI [0.000 0.027]) on MDD group status emerged. Instead, no indirect effect (β= -.01, SE=.01, p = 0.20, 95% CI [-0.034 0.007]) or total effect (β= -0.00, SE=. .012, p = 1.00, 95% CI [-0.022 0.023]) of the LPP_{resid} through anhedonia emerged.

Similarly, the path model on $Delta_{resid}$ fit well the data (CFI = 1.00; RMSEA = 0.00) and showed a direct effect of $Delta_{resid}$ (β = -.18, SE = .09, p = 0.04, 95% CI [-0.348 -0.007]) but not a significant indirect (β = -.11, SE =.12, p = .35, 95% CI [-0.329 0.128]) or total effect (β = -29, SE =.13, p = 0.03, 95% CI -0.524 0.008])[6] through anhedonia.

[6] The p-value was significant, but the confidence interval included 0. The p-values are computed assuming the Z-statistic comes from a standard normal distribution, which for most mediation-related quantities is not true in finite samples. The bootstrap confidence intervals are the most accurate because they make few assumptions about the sampling distribution of the quantity of interest. Hence, these analyses rely entirely on the bootstrap confidence intervals (Hayes & Scharkow, 2013).

4.6.4 Discussion

These additional analyses aimed at examining whether, similarly to Study 1, anhedonia was a significant mediator of the association between neural responses (LPP and delta power) to pleasant images and group status (MDD, controls).

Unlike the results of Study 1, the link between electrocortical responses to pleasant images and MDD group status was not mediated by anhedonia scores. In Study 1, anhedonia mediated the link between blunted delta power to appetitive images in dysphoria, supporting the hypothesis that delta activity reflects the activation of approach motivation. Considering that the present study was conducted on individuals with clinical depression, it could be hypothesized that anhedonia drives blunted electrocortical responses to appetitive cues at initial and subclinical phases of depression, while in participants with already full-blown depression these reduced neural responses might be related to a complex interaction of multiple variables that were not considered in this study. In addition, this null finding could be due to the intake of psychotropic medications in the experimental group. Taken together, future studies should include further measures of positive affect as well as other relevant symptom dimensions.

CHAPTER V

STUDY 3: DEPRESSIVE SYMPTOMS AND COGNITIVE CONTROL: THE ROLE OF AFFECTIVE INTERFERENCE[7]

5.1 Preface to Study 3

Study 1 employed an advanced time-frequency approach to explore affective and cognitive processing of emotional (pleasant, unpleasant) pictures in individuals with dysphoria. What emerged was a reduced affective disposition to appetitive images and greater cognitive processing of unpleasant images in dysphoria. Then, Study 2 focused on the exploration of approach motivation in clinical depression and replicated findings from Study 1.

As described in Chapter I, although depressive symptoms seem to be characterized by altered cognitive function, it remains unclear whether these deficits are selective for affective contexts or extend to non-affective conditions. Hence, Study 3 aimed at exploring the **influence of the Positive and Negative Valence Systems on the Cognitive Systems** in relation to depressive symptoms with task-switching paradigm designed in a non-emotional and an emotional version. The current work was conducted online because of the pandemic, thus only behavioral data were collected and, instead of dividing the sample into two groups based on diagnostic status, continuous levels of depressive symptoms were considered.

[7] Results from this study have been published in **Dell'Acqua, C.,** Messerotti Benvenuti, S., Vallesi, A., Palomba, D., & Ambrosini, E. (2022). Depressive symptoms and cognitive control: the role of affective interference. *Cognition and Emotion*, 1-15.

5.2 Abstract

As detailed in Chapter I, depressive symptoms are characterized by reduced cognitive control. However, whether depressive symptoms are linked to difficulty in exerting cognitive control in general or over affective content specifically remains unclear. To better differentiate between affective interference or general cognitive control difficulties in individuals with depressive symptoms, a non-emotional (cold) and an emotional (hot) version of a task-switching paradigm was employed in a nonclinical sample of young adults (N = 82) with varying levels of depressive symptoms. Depressive symptoms were linked to greater difficulties in exerting cognitive control in complex situations (mixed-task blocks) compared to simple and semiautomatic situations (single-task blocks) in both task versions. Moreover, greater depressive symptoms were associated with longer latencies in the emotional version of the task across all trial types. Thus, the emotion-specific effect was not modulated by the degree of cognitive control required to perform the task and was also not influenced by the emotional category (pleasant, unpleasant). In sum, depressive symptoms were characterized by a general difficulty to exert cognitive control in both emotional and non-emotional contexts and by greater difficulty in even simple attentional processing of emotional material. This study granted novel insights on the extent of RDoC Cognitive Systems functioning in emotional and non-emotional contexts for individuals with depressive symptoms.

5.3 Introduction

Difficulties in cognitive control have been acknowledged as relevant to the development and maintenance of depressive symptoms (e.g., De Raedt & Koster, 2010; Disner et al., 2011; Keller et al., 2019). Indeed, although the core symptoms of depression are sustained negative affect and anhedonia, the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association, 2013) has included a "diminished ability to think or concentrate" as a diagnostic criterion for depression. Depression has been linked to difficulties in cognitive control, a set of high-order functions that allow people to flexibly achieve goal-directed behaviour (Kashdan & Rottenberg, 2010; Meiran et al., 2011; Stange et al., 2017). Regarding the Research Domain Criteria (RDoC) detailed in Chapter I, cognitive control deficits suggest a reduced functioning of the Cognitive Systems of the RDoC.

Moreover, a recently emerging approach, especially in the study of depressive symptoms, is to differentiate cognitive control functions exerted in emotional contexts (*hot* functions) from general non emotional cognitive control functions (*cold* functions; Fossati, 2018; Roiser & Sahakian, 2013; Salehinejad et al., 2021). This distinction conceptualizes cognitive control on a continuum, where each function can be relatively hot or cold depending on the context (Salehinejad et al., 2021).

A wealth of evidence has demonstrated that individuals with depressive symptoms are characterized by broad **cognitive control difficulties** (Bortolato et al., 2014; Dotson et al., 2020; Rock et al., 2014; Snyder et al., 2013). Cognitive inflexibility has been documented in individuals with different levels of depressive symptoms across different non emotional neuropsychological tests (e.g., Harvey et al., 2004; Lin et al., 2014; Moritz et al., 2002; Parkinson et al., 2020; Rokke et al., 2002; Wilkinson & Goodyer, 2006). Of note, the effect sizes of cognitive control difficulties were larger for older adults or individuals with clinical

depression (Dotson et al., 2020). Indeed, other studies have not found depressive symptoms to have a significant effect on cognitive inflexibility in samples of adolescents and young adults without clinical depression (Goodall et al., 2018; Vilgis et al., 2015). Some researchers who have specifically employed computerized task-switching paradigms in studies on depression have found longer latencies in switch trials compared to repeat trials (i.e., greater switch costs; Hoffmann et al., 2017), whereas others have failed to find switch cost differences in individuals with depression and healthy controls (Meiran et al., 2011; Remijnse et al., 2013; Whitmer & Gotlib, 2012).

Notably, a separate line of research has focused on the study of cognitive control in *hot* contexts in relation to depressive symptoms (e.g., Joormann & Vanderlind, 2014; Koster et al., 2011). In particular, the preferential processing of unpleasant stimuli across all domains of information processing is thought to influence cognitive control performance in individuals with depressive symptoms (Gotlib & Joorman, 2010; Joormann & Vanderlind, 2014; LeMoult & Gotlib, 2019). Using various paradigms, several studies have shown that depressive symptoms or the risk of developing depression was related to difficulties in switching away from or inhibiting unpleasant stimuli (i.e., angry and sad faces, threatening and sad scenes and words; Epp et al., 2012; Everaert et al., 2017; Goeleven et al., 2006; Lisiecka et al., 2012; Murphy et al., 2012; Wen & Yoon, 2019) and updating working memory when the content was unpleasant (Joormann, 2010; Levens & Gotlib, 2010), corroborating the view that unpleasant content interferes with cognitive control functions (Gotlib & Joorman, 2010; Joormann, 2010; LeMoult & Gotlib, 2019;). Moreover, greater difficulties in switching away from unpleasant stimuli have also been related to psychological aspects linked strictly to depressive symptoms, such as ruminative thinking (Genet et al., 2013), reduced adaptive emotional regulation strategies (i.e., reappraisal; Grol & De Raedt, 2021; Malooly et al., 2013), and resilience (Grol & De Raedt, 2018). Additionally, a study showed that individuals with depressive symptoms,

compared to those in a control group, had poorer switching abilities for unpleasant stimuli but better switching abilities for pleasant stimuli (Deveney & Deldin, 2006). Instead, longer latencies in switching away from pleasant stimuli than from unpleasant stimuli were documented in individuals with clinical depression (Quigley et al., 2020). Furthermore, affective switching difficulties for both pleasant and unpleasant content were found in individuals with depression (De Lissnyder et al., 2012) and depression in remission (Lange et al., 2012) and were found to prospectively predict increased depressive symptoms in a remitted sample (Demeyer et al., 2012).

Generally, valence-specific effects in hot task-switching paradigms in relation to depressive symptoms are still unclear. For instance, valence-specific effects on pleasant stimuli have not been thoroughly explored. Considering the evidence on the reduced processing of pleasant stimuli in individuals with depressive symptoms (e.g., Mennella et al., 2015; Messerotti Benvenuti et al., 2015, 2019; Nandrino et al., 2004; Shane & Peterson, 2007; for a review, see Winer & Salem, 2016), the investigation of cognitive control over both unpleasant and pleasant stimuli would allow a better understanding of potential valence-specific cognitive control difficulties in individuals with depressive symptoms. In terms of RDoC functioning, the study of valence-specific effects on cognitive control would allow the study of the influence of the Positive and Negative Valence Systems on Cognitive Systems functioning.

To date, only a limited number of studies have employed both *cold* and *hot* versions of the same paradigm to investigate cognitive control in people with depressive symptoms. These few studies have linked depression to a selective difficulty in cognitive control in emotional task versions compared to non-emotional task versions (Lo & Allen, 2011; Murphy et al., 2012). However, the employment of paradigms tackling distinct processes (e.g., go/no-go, internal shifting task) and the fact that the investigation was restricted exclusively to clinical

samples make reaching a consensus hard regarding the distinct involvement of *cold* and *hot* functions in people with depressive symptoms.

Hence, despite the evident involvement of cognitive control processes in modulating depressive symptoms, whether depressive symptoms are linked to a general difficulty to exert cognitive control or to a selective difficulty to exert cognitive control over emotional content remains unclear (Grahek et al., 2018; Joorman & Tanovic, 2014). On one hand, although cognitive control in cold contexts does not directly involve emotional processing, several researchers have suggested it may facilitate the implementation of emotional regulation strategies and protect performance in hot contexts, counteracting the risk conferred by depression-related emotion-processing biases (Roiser et al., 2012; Roiser & Sahakian, 2013; Whitmer & Gotlib, 2012). Therefore, depressive symptoms may be associated with general cognitive control difficulties that, in turn, affect control over emotional information. On the other hand, a classical view of cognitive processes in individuals with depressive symptoms postulates that negative schemas generate a processing advantage for unpleasant stimuli, leading to the altered encoding and processing of all other information (Beck & Bredemeier, 2016; Clark & Beck, 2010; Siegle et al., 2002). Therefore, individuals with depressive symptoms may display difficulties in switching away from emotional stimuli in hot contexts not because of impaired switching mechanisms, but because of enhanced reactivity to emotional stimuli that impact cognitive control functions (e.g., Lo & Allen, 2011).

To better understand whether depressive symptoms are characterized by selective difficulties in emotional contexts or by general cognitive control difficulties, studies comparing performance in cold and hot versions of the same paradigm are warranted (Quigley et al., 2020). To this end, we employed both a cold and a hot version of a task-switching paradigm in a nonclinical sample of young adults with varying levels of depressive symptoms. This paradigm requires participants to perform tasks either in isolation (single-task blocks) or in an

intermixed fashion (mixed-task blocks, composed of switch and repeat trials; Meiran, 2010; Monsell, 2003). This paradigm evaluates different aspects of cognitive control, including the cost of switching from one rule to the other, the cost of keeping multiple task sets active, and the disengagement from a previous task set and stimulus (Kiesel et al., 2010; Meiran, 2010; Monsell, 2003). Specifically, two distinct and dissociable processes can be assessed with this paradigm: (a) the so-called "switching cost," namely the process of task-set reconfiguration, a phasic and transient activation required to switch between tasks, assessed based on the performance difference between switch and repeat trials; and (b) the so-called "mixing cost," a sustained process reflecting the increase in active demands due to the concurrent maintenance and management of multiple task sets, assessed based on the performance difference between repeat and single trials (Monsell, 2003; Rubin & Meiran, 2005).

Because this was the first study to directly compare the participants' performance on both hot and cold versions of a task-switching paradigm in relation to depressive symptoms, the main hypothesis was twofold. Based on the reviewed literature linking depressive symptoms to a general reduction in cognitive control abilities, we expected more depressive symptoms to be associated with cognitive control difficulties in both task versions. Additionally, based on the few studies that have linked depression to a selective difficulty in affective cognitive control (Lo & Allen, 2011; Murphy et al., 2012), we expected these cognitive control difficulties to be more pronounced (i.e., longer response times) in the emotional compared to the non-emotional task version. Moreover, specifically for the emotional version of the task, we expected higher levels of depressive symptoms to be related to a valence-specific bias, with longer RTs in switching away from unpleasant stimuli compared to pleasant stimuli.

5.4 Methods

Participants

Ninety-five Caucasian young adults (35 males; M_{age} = 25.4 years, SD_{age} = 2.9) were recruited through local advertisements or by word of mouth and voluntarily took part in the online study. Exclusion criteria included the presence of any mental disorder and the use of psychotropic drugs. Furthermore, only individuals between the ages of 18 and 35 years were recruited because young adults with depressive symptoms already show poor cognitive control, and this has been suggested to be an early risk factor for depression (Goodall et al., 2018). Of the total sample of 95, seven volunteers were excluded from the study after an anamnestic interview because they reported clinical depression or anxiety in pharmacological treatment (n = 4) and substance abuse (n = 3). Individuals who reported a diagnosis of clinical depression were excluded because the study was conducted online and confirming the diagnosis was not possible through a clinical interview (e.g., structured clinical interview for *DSM-5*). Another reason for not including those on medications or with diagnoses was that most of the participants had only subthreshold levels of depression; therefore, including seven participants with clinical depression, anxiety, or substance abuse would have led to an unbalanced sample. In addition, six participants could not complete the task due to technical issues. The final sample consisted of 82 participants (30 males; M_{age} = 25.5 years; SD_{age} = 3.0), medically healthy and free from psychotropic medications, as assessed with an ad hoc anamnestic interview. Because it was not possible to assess the presence of a depressive disorder through clinical interviews, depressive symptoms were evaluated on a continuum. Moreover, the examination of subclinical depressive symptoms provides an advantage because it allows isolation of the effects of interest without any alterations produced by the use of antidepressant medications or the chronicity of the disorder. The participants were not compensated for their participation. This study was conducted with adequate understanding and written consent of

the participants in accordance with the Declaration of Helsinki and was approved by the Ethics Committee, University of Padua (Protocol No. 3640).

Sensitivity power analysis

Our sample consisted of a convenience sample recruited via online advertisements through social networks or identified via researchers' personal networks. The method introduced by Westfall et al. (2014) was used to perform a sensitivity power analysis for a fully crossed linear mixed-effects model, assuming participants, stimuli, and residual variance partitioning coefficients of .25, .05, and .7, respectively, as estimated conservatively from some recent unpublished studies with a similar design to ours. The other variance partitioning coefficients were set to 0, because those effects were not included in the models we tested. This analysis revealed that the sample size (82 participants and eight stimuli, see below) was large enough to detect a small effect size (Cohen's d = 0.15) with a power of .80. However, this approach is not fully adequate for complex mixed-effects models such as the one used in this work, but it nonetheless provided a useful estimation of the so-called minimal statistically detectable effect for our study (i.e., the lower bound of the range of effect sizes that can be detected). Indeed, to the best of our knowledge, to date, no accepted analytical approaches have been ascertained to compute statistical power accurately for such models. To provide another estimate of our minimal statistically detectable effect, which could also facilitate comparison with future studies using more standard analytical approaches, a sensitivity power analysis in G*Power for a repeated measure analysis of variance (ANOVA) for the domain by condition interaction, assuming a correlation between repeated measures of .85, was performed. This analysis revealed that the sample size was large enough to detect a small effect size (d = 0.17, corresponding to η_p^2 = .007) with a power of .80. Notably, however, G*Power (and to the best of our knowledge, all other software commonly used to compute power) does not support a

power calculation for general linear model effects including both multiple within-subjects factors and continuous covariates.

Data were analysed using R (Version 1.2.5001; R Core Team, 2012), the stats package (R Core Team, 2013), lme4 (Bates et al., 2015), and lmerTest (Kuznetsova et al., 2017).

Self-report measure of depressive symptoms

Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Italian version by Ghisi et al., 2006). The BDI-II scale is a reliable and valid self-report questionnaire developed to assess the severity of depressive symptoms over the previous 2 weeks. Specifically, the BDI-II is composed of 21 items, each based on a 4-point Likert scale, and scores range from 0 to 63, with higher scores indicating greater depressive symptoms (Ghisi et al., 2006). Internal consistency was high for the 21 items of the BDI-II (Cronbach's $\alpha = .92$).

Task-switching paradigm and behaviour data reduction

Cognitive control in cold and hot contexts was assessed with two versions (emotional and non-emotional) of a task-switching paradigm adapted from Rubin and Meiran (2005) and created in the PsychoPy software (Peirce et al., 2019). Figure 5.1 graphically represents the task design. Each version consisted of a total of four single-task blocks, each comprising 30 trials, and two mixed-task blocks, each comprising 40 trials. A "sandwich-like" design was adopted: Two single-task blocks, each comprising 10 practice trials, were followed by two mixed-task blocks, comprising 10 practice trials, and then again by two single-task blocks. The order of single-task blocks was counterbalanced across participants. Half of the participants started with the hot version, and the other half with the cold one.

The single-task blocks required the participants to perform two types of subtasks, one at a time in different blocks. In the mixed-task blocks, the participants had to categorize the target stimulus based on a categorization rule indicated by a cue, which changed unpredictably trial by trial. The task could be either repeated (repeat trials) or switched (switch trials) based on a pseudorandom order. Within the single-task blocks, a trial started with the presentation of a black fixation cross on a grey background positioned at the centre of the screen for 500 ms, followed by the presentation of the target stimulus until the participants produced a response. The inter-trial interval included a black fixation cross on a grey background positioned at the centre of the screen, and its duration was either 500 or 700 ms. Within the mixed-task blocks, before stimulus presentation, a visual cue that indicated the task to be performed appeared at the centre of the screen for 1,000 ms.

The stimuli included in the cold version of the paradigm were two geometric shapes (triangle and circle) coloured in red or blue, presented individually at the centre of the screen on a grey background. The participants were asked to respond according to either the shape or the colour of the target stimulus. The single-task blocks required the participants to categorize the target stimulus selectively based on either colour or shape. Instead, the mixed-task blocks included the categorization of the target (either a "colour task" or a "shape task") based on a cue. The participants had to press the left arrow button to indicate either a triangle or a blue shape and the right arrow button to indicate either a circle or a red shape.

The stimuli included in the hot version of the paradigm were four coloured images of faces with no hairline from the A series of the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998) selected from a validation study of the database's picture set (Goeleven et al., 2008)[8], presented individually at the centre of the screen on a grey background. The stimuli included two happy faces (one female, one male) and two sad faces (one female, one

[8] The KDEF images included in the study were: F26SA, M17SA, F26HA, M17HA.

male) selected from a validation study of the database's picture set based on intensity ratings (happy, $M = 6.34$, $SD = 1.64$; sad, $M = 6.55$, $SD = 1.70$) and arousal ratings (happy, $M = 3.7$, $SD = 2.85$; sad, $M = 4.0$, $SD = 1.84$; Goeleven et al., 2008). The happy and sad faces did not differ in arousal ratings ($p = .57$). The participants were asked to respond according to the emotion or gender of the face. Particularly, the single-task blocks required the participants to categorize the target stimulus selectively based on either the emotion or gender of the face. The mixed-task blocks included the categorization of the target (as either an "emotion task" or a "gender task") based on a cue. The participants had to press the left arrow button to indicate either an unpleasant stimulus or a female face and the right arrow button to indicate either a pleasant stimulus or a male face.

The task was self-paced, and RTs and accuracy were measured. The first trial of each block was excluded from the analysis. Incorrect trials (3.49% of all trials) and RTs longer than 3,000 ms or shorter than 100 ms (0.41% of correct trials) were also excluded from the analyses. The RTs were then inversely transformed (−1,000/RTs in ms) to produce the normal distribution required to conduct linear mixed-effects models, because the RT distributions were heavily skewed (skewness = 2.61) as typically observed (e.g., Schmidt & Weissman, 2016). The reliability of the transformed RTs in the single, repeat, and switch trials in the cold and hot tasks was evaluated by computing split-half correlations corrected with the Spearman-Brown formula (2,000 random splits).

General procedure

This study was conducted within an extensive research project on vulnerability to depression, and self-report measures of emotional regulation, anxiety, and heart rate were collected but not analysed in this work. First, each participant completed an online survey administered via Google Modules that included informed consent, a sociodemographic and anamnestic interview, and the BDI-II self-report questionnaire. Subsequently, the participants

received a link to complete the task-switching paradigm on their computers through the Pavlovia.org online platform. The participants were instructed to find a quiet and comfortable room free of distractions and to avoid completion of the task during night hours (completion time was checked on the output data) and the consumption of alcohol or caffeine in the hours preceding the experiment.

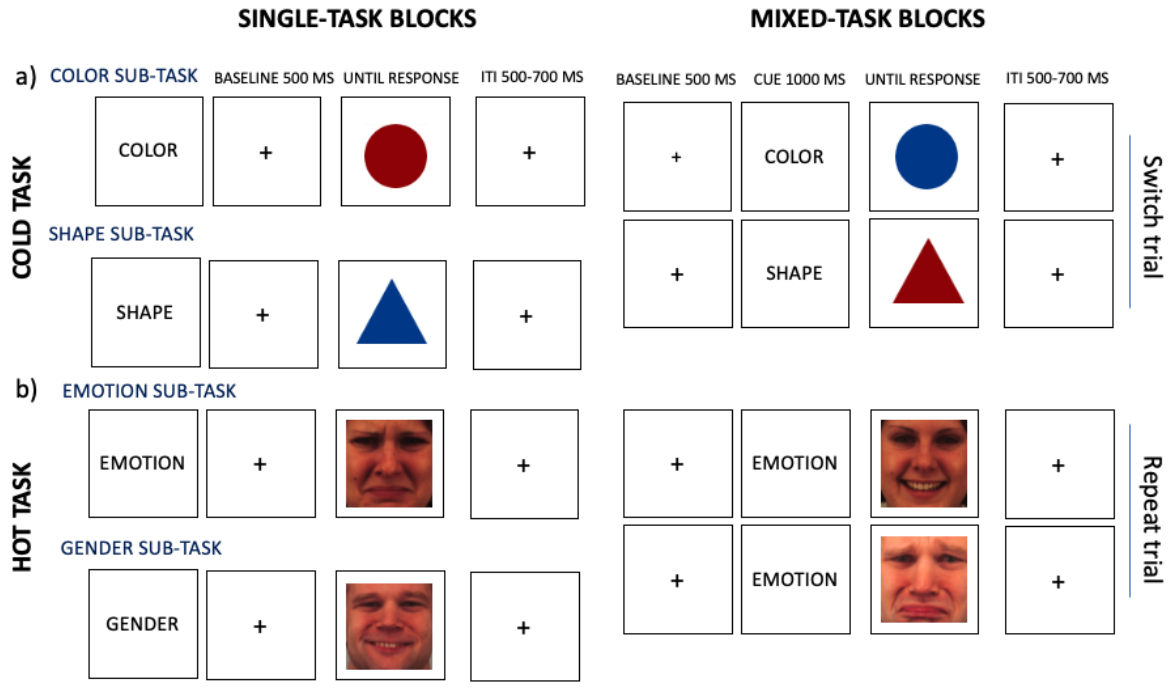

Figure 5.1 Task-switching paradigms. A) Non-emotional (cold) paradigm. On the left single-task blocks, where the categorization of the target is based on one feature (either colour or shape). On the right mixed-task blocks, where the task varies based on a cue presented for 1000 ms before stimuli onset and each trial can be either a repeat trial or a switch B) Emotional (cold) paradigm. On the left single-task blocks, where the categorization of the target is based on one feature (either emotion or gender). On the right mixed-task blocks, where the task varies based on a cue presented for 1000 ms before stimuli onset and each trial can be either a repeat trial or a switch.

Statistical analyses

Statistical analyses were performed in R (Version 1.2.5001; R Core Team, 2012). The effects of depressive symptoms on cognitive control in both cold and hot contexts were investigated by performing a linear mixed model with the RTs as the dependent variable using the lmer function from the lmerTest library (Kuznetsova et al., 2017). Specifically, we tested for the effects of BDI-II scores, domain (emotional or hot, non-emotional or cold), and

condition (trial types: single, repeat, switch) and all their two- and three-way interactions as fixed effects of primary theoretical interest.

Mixed-effects models have several advantages over traditional linear model analysis (i.e., repeated-measures ANOVA). Because this analysis was conducted at the trial level, it accounted for variability at the individual level and avoided potential bias due to data aggregation (i.e., comparing mean values; Singmann & Kellen, 2019). Moreover, unlike general linear models, mixed-effects models are very robust at handling missing data and unbalanced data sets (Baayen et al., 2008; Quène & van den Bergh, 2008).

The simplest, best linear mixed-effects model to fit the dependent variable (RTs) was determined by iteratively comparing simpler models (starting from the null model) with more complex models using the ANOVA function (R stats library), which provided the chi-square statistics and the related *p* value of the likelihood ratio test. The Bayes factors in favour of the simpler models (BF_{12}) using the BayesFactor package (Morey et al., 2015) were also computed[9]. Particularly, the models were as follows: (a) a null model that included only the participant ID and experimental stimuli as random intercepts and the trial order as both a fixed effect and a by-participant random slope to control for possible confounding time-on-task effects, (b) more complex models that also included the main fixed effects of condition, domain, and BDI-II scores, (c) more complex models that also included their two-way interactions, and (d) the full-factorial model that also included their three-way interaction. After this model-building procedure, the statistical significance of the fixed effects included in the final model was assessed as detailed below.

[9] The Bayes factor can be interpreted as a measure of the strength of evidence in favor of one model over another. In line with an influential classification scheme for interpreting Bayes factors, values greater than 3, 10, 30, and 100 are considered, respectively, moderate, strong, very strong, and extreme evidence (Lee & Wagenmakers, 2014; Jeffreys, 1961).

The final model was refitted after we excluded outliers, which were identified as observations with absolute standardized residuals greater than 3 (Ambrosini et al., 2015). For the fixed effects, the estimated coefficient (*b*), standard error (*SE*), and *t* values for each parameter included in the final model were reported. In addition, the *p* values obtained through the Satterthwaite approximation (implemented in the lmerTest library) were reported. A *p* value of .05 was the cut-off for statistical significance.

Regarding the specific valence-effects within the emotional version of the paradigm, a separate linear mixed-effects model was conducted to explore the potential influences of the valence (pleasant, unpleasant) of the previous trial in simple and complex cognitive control conditions (i.e., trial types) on the RTs as a function of the participants' BDI-II scores. Specifically, we tested BDI-II, condition (trial types: single, repeat, switch), valence of the previous trial (pleasant, unpleasant), and their two- and three-way as fixed factors of primarily theoretical interest. The same model-building procedure detailed above was conducted to identify the simplest, best linear mixed-effects model to fit the dependent variable (RTs), and statistical analysis of the final model was conducted as detailed above. The same analysis was conducted with the valence of this trial.

Accuracy was not analysed because it was very high (> 96%), indicating the participants' performance was at the ceiling level. Indeed, 68 of the 82 participants (corresponding to approximately 83% of the sample) had perfect accuracy in at least one experimental condition. This prevented the reliable estimation of the experimental effects on accuracy. Nonetheless, we checked for the presence of a speed–accuracy trade-off by correlating the participants' mean RTs and accuracy. This analysis revealed a near-zero correlation, $r = .001$, $t(80) = 0.01$, $p = .990$, indicating the absence of a speed–accuracy trade-off in our sample.

5.5 Results

Descriptive statistics

The average BDI-II score of the sample was 10.7 (*SD* = 9.2), and the scores ranged from 0 to 43, with a skewness of 1.48 and a kurtosis of 2.04 (Figure 5.2). Regarding the RTs for each trial type (single, repeat, switch), domain (cold, hot), and accuracy, the descriptive statistics are displayed in Table 5.1. The reliability estimates of the inverse-transformed RTs were very high (median value across the 2,000 random splits > 0.95 in all cases), indicating the adequacy of the online assessment of task-switching ability.

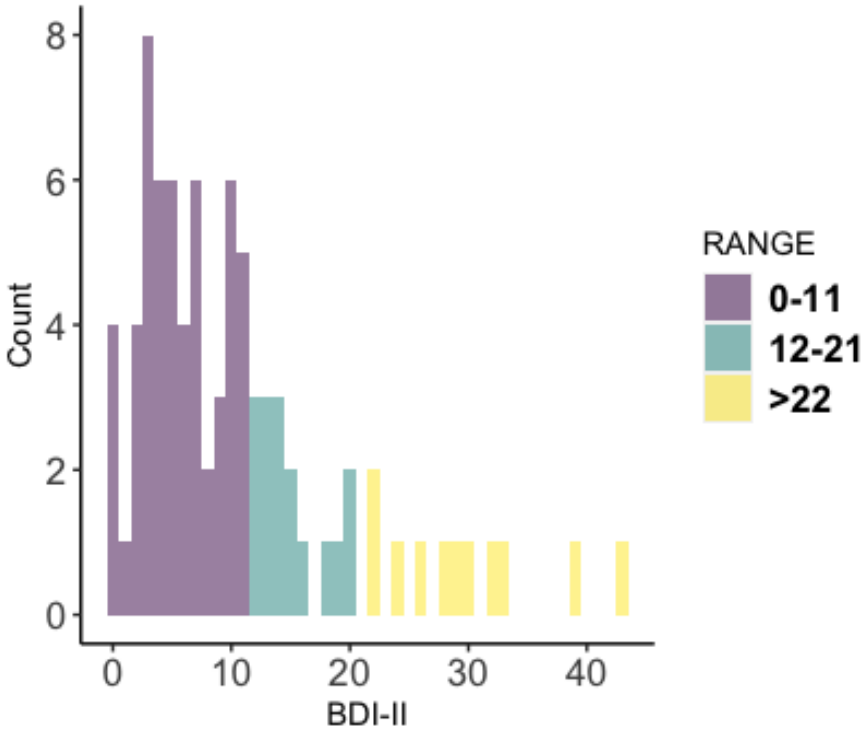

Figure 5.2 Distribution of Beck Depression Inventory (BDI-II) scores across the sample.

Table 5.1. Descriptive statistics for behavioural data.

	Single		Repeat		Switch	
	M	*SD*	*M*	*SD*	*M*	*SD*
COLD TASK						
Response times (ms)	503	93.2	685	198	763	232
Accuracy (%)	98	3.9	97	2.6	95	2.2
HOT TASK						
Response times (ms)	606	106	763	208	852	252
Accuracy (%)	97	6.1	97	2.1	94	2.6

Note. M = mean; SD = standard deviation; ms = milliseconds

Depressive symptoms and task performance in the cold and hot task versions

The model-building procedure revealed that the inclusion of the three-way interaction (Condition × Domain × BDI-II scores) was not justified, $\chi^2(2) = 0.12$, $p = .94$; $BF_{12} = 685$. Instead, the simplest, best linear mixed-effects model to fit the dependent variable (RTs) was the model that included the main fixed effects (condition, domain, BDI-II), their two-way interactions, the fixed effect for trial and its random by-participant slope, and the participants and stimuli as random intercepts. The R notation for the final model was as follows*:*

*lmer(RTs ~ trial + domain * condition + domain * BDI-II + condition * BDI-II + (trial/participant) + (1/stimulus)).*

The marginal R^2 of the final model, which represents the variance explained by the fixed effects, was .18; the conditional R^2, which is the variance explained by both the fixed and random effects, was .44. The statistics for the fixed effects of the final model are displayed in

Table 5.2. A significant main effect of trial emerged, $F(1, 77) = 21.47$, $p < .001$, reflecting an overall decrease of RTs as the experimental session progressed. Moreover, a significant main effect of domain emerge, $F(1, 22) = 178.70$, $p < .001$, reflecting overall longer RTs for the emotional (i.e., hot) compared to the non-emotional (i.e., cold) task version. Additionally, a significant main effect of condition emerged, $F(2, 31605) = 920.63$, $p < .001$, with longer RTs for the switch trials compared to both the repeat and single trials and longer RTs for the repeat trials compared to the single trials (all ps $< .001$). A significant interaction between domain and condition (Figure 5.3) also emerged, $F(2, 31067) = 115.68$, $p < .001$, showing that the domain effect, that is, the increase in RTs for the emotional (i.e., hot) compared to the non-emotional (i.e., cold) task version, was smaller for both the repeat and switch trials compared to the single trials ($p < .001$), whereas no significant difference was observed for the domain effect between the repeat and switch trials ($p = .607$).

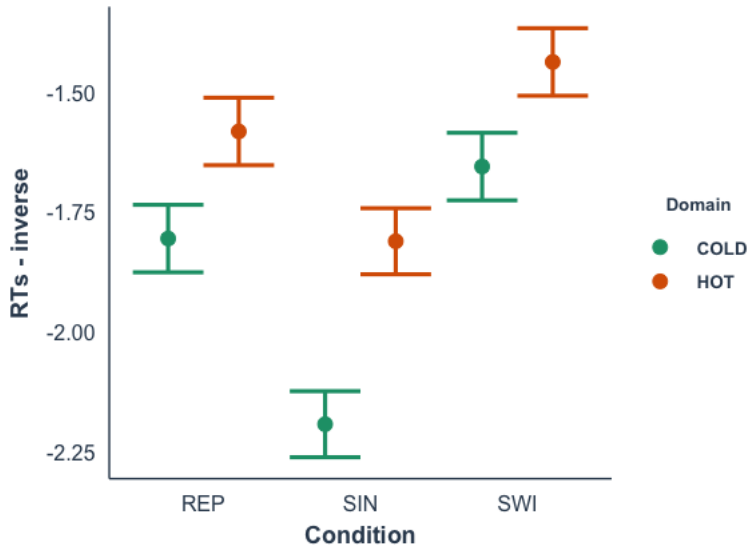

Figure 5.3 Interaction effect of Condition and Domain on response times (RTs). Error bars represent Ninety-five % confidence bands for each Condition. Note. SIN = single trials; REP = repeat trials; SWI = switch trials.

Moreover, the BDI-II × Domain interaction was significant, $F(1, 1242) = 14.95$, $p < .001$, showing a BDI-II-dependent increase in RTs that was stronger for the emotional (i.e.,

hot) than the non-emotional (i.e., cold) task version (Figure 5.4, Panel b). The BDI-II × Condition interaction was also significant, $F(2, 31066) = 13.23$, $p < .001$, showing that the BDI-II-dependent increase in RTs was stronger for both the switch and repeat trials compared to the single trials (both $ps < .001$), whereas it did not significantly differ between the switch and repeat trials ($p = .231$; Figure 5.4, Panel a).

Due to the nonnormality of the BDI-II distribution, a control analysis was performed to verify the robustness of the described results and control for possible biases due to the influence of participants with high BDI-II values. To this aim, the same linear mixed-effects model was conducted after log transforming the BDI-II scores. The control analysis confirmed all the effects described above.

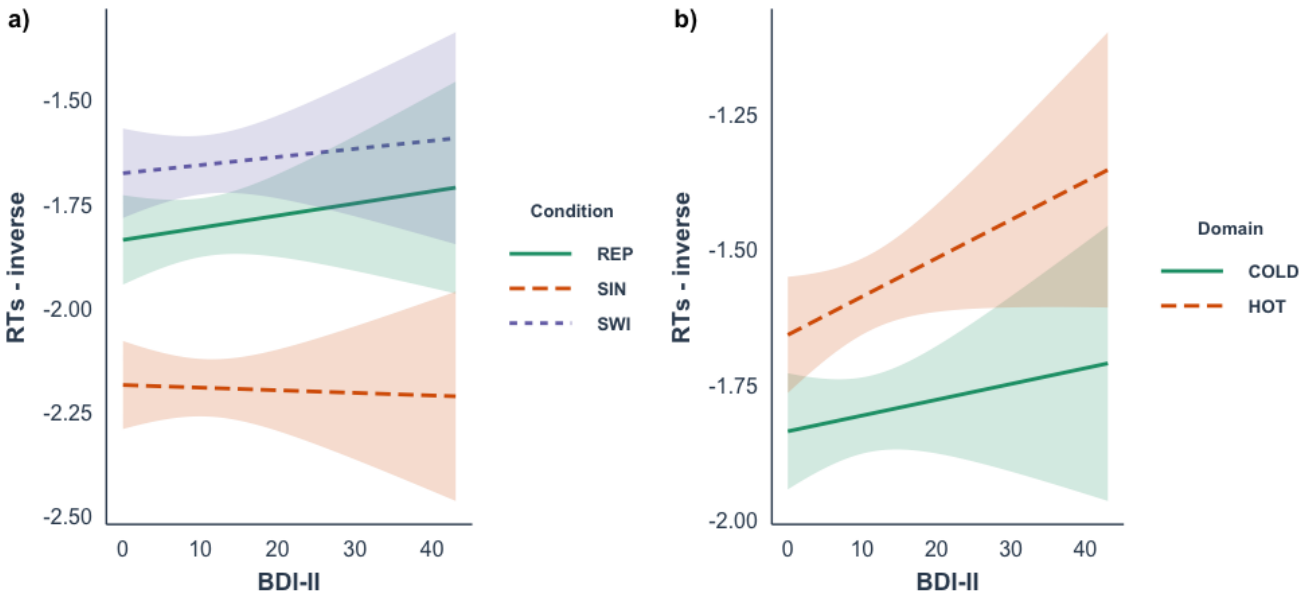

Figure 5.4 Panel a) Interaction effect of BDI scores and Condition (Single, Repeat, Switch) on response times (RTs). Ninety-five % confidence bands for each Condition are presented in different colours. Note. REP = repeat trials; SIN = single trials; SWI = switch trials. Panel b) Interaction effect of BDI scores and Domain (cold or hot) on response times (RTs). Ninety-five % confidence bands for cold and hot task versions are presented in different colours.

Depressive symptoms and valence-specific effects

The model-building procedure revealed that the inclusion of the three-way interaction (Condition × Valence × BDI-II) was not justified, $\chi^2(2) = 1.99$, $p = .37$; $BF_{12} > 10^5$. Moreover, the inclusion of the valence effect and its interactions with either BDI-II or condition was not justified (all ps > .3; all BF_{12}s > 41). Instead, the simplest, best linear mixed-effects model to fit the dependent variable (RTs) was the model that included the main fixed effects of condition and BDI-II, their two-way interaction, the fixed effect for trial, and its random by-participant slope, and the participants and stimuli as random intercepts. The R notation for the final model was as follows: *lmer(RTs ~ trial + condition * BDI-II + (trial/participant) + (1/stimulus))*.

The marginal and conditional R^2 of the final model were, respectively, 0.09 and 0.39. The analysis confirmed the significant main effect of condition, $F(2, 14938) = 335.89$, $p < .001$, and Condition × BDI-II interaction, $F(2, 14956) = 9.43$, $p < .001$, which replicated the pattern of results in the previous analysis. Again, a control analysis performed with log-transformed BDI-II scores confirmed the general pattern of the results.

Furthermore, a similar control analysis was performed to verify whether the valence modulated the reported result. Again, however, the analysis revealed that the more complex model including the interaction with the valence predictor was not justified, $\chi^2(6) = 11.26$, $p = .08$; $BF_{12} > 10^4$.

Table 5.2. Estimated parameters of the final linear mixed-effect model of response times with a baseline of Single trials and Cold task version.

Fixed Effects	**Estimate (SE)**	***t***	***p***
Intercept	-2.210 (.055)	-40.000	**<.001**
Domain	.380 (.020)	18.790	**<.001**
Condition - Repeat	.359 (.013)	27.670	**<.001**
Condition - Switch	.521 (.013)	39.930	**<.001**
BDI	.000 (.004)	-.020	.986
Domain:ConditionRepeat	-.165 (.014)	-11.740	**<.001**
Domain:ConditionSwitch	-.174 (.014)	-12.250	**<.001**
Domain:BDI	.004 (.001)	3.870	**<.001**
ConditionRepeat:BDI	.004 (.001)	4.690	**<.001**
ConditionSwitch:BDI	.002 (.001)	3.200	**.001**

Note. SE = standard error; BDI-II = Beck Depression Inventory-II; Significant effects are displayed in bold.

5.6 Discussion

This study was the first to employ the same task-switching paradigm in emotional (i.e., hot) and non-emotional (i.e., cold) versions to assess whether the presentation of emotional material in individuals with greater depressive symptoms would influence cognitive control. We expected more depressive symptoms to be associated with general cognitive control difficulties in both task versions. Alternatively, based on the few studies that have linked depression to a selective difficulty in affective cognitive control (Lo & Allen, 2011; Murphy et al., 2012), we expected higher levels of depressive symptoms to be associated with selective difficulties in the hot contexts. Moreover, specifically for the emotional version of the task, we

expected a valence-specific bias, with longer RTs in switching away from unpleasant stimuli compared to pleasant stimuli.

For the whole sample, condition had a significant effect, namely, as expected in a task-switching paradigm, a difference among the three task conditions, with longer RTs in the switch trials than in repeat (i.e., switching cost) and single trials and longer RTs in repeat than in single trials (i.e., mixing cost). These differences reflect the distinct processes that can be disentangled in a task-switching paradigm, namely a switching cost, determined by the activation of a task set reconfiguration process that is not required in repetition trials, and a general mixing cost, determined by the need to keep multiple task sets active during the mixed block compared to the single block condition (Monsell, 2003; Rubin & Meiran, 2005). However, depressive symptoms were related to greater difficulties in exerting cognitive control in the complex situations (switch and repeat trials) than in the simple and semiautomatic situations (single trials), in both the emotional and non-emotional task versions. Hence, the BDI-II scores were not differentially related to the switch and repeat trials, presenting a similar pattern for both trial types. This indicates that the individuals with greater depressive symptoms did not show the typical facilitation effect for the repeat trials compared to the switch trials. Consequently, mixing cost, namely the difference between the repeat and single trials, increased with the BDI-II scores. Although the switching cost has been widely studied as a measure of cognitive control abilities (e.g., Rubin & Meiran, 2005), the study of mixing cost has been fairly neglected, and this is the first study on depressive symptoms to include single-task blocks. However, several researchers have argued that mixing cost may represent an accurate measure of cognitive control in conditions requiring sustained attention and the management of competition between task sets (Ambrosini et al., 2019; Marì-Beffa et al., 2012; Marì-Beffa & Kirkham, 2014; Meiran, 2005). Therefore, in this study, depressive symptoms were associated with a **general difficulty in the maintenance of cognitive control** (i.e.,

mixing cost) due to a diminished differentiation between the switch and repeat trials, leading, in turn, to reduced switching costs. However, this does not necessarily indicate that individuals with greater depressive symptoms do not show difficulties in phasic task-set reconfiguration, because they might also be likely to employ a task-set reconfiguration process in both switch and repeat trials indiscriminately. In the context of computerized task-switching studies on depression, these results are in contrast with some previous studies that reported specific switching difficulties in depression (e.g., Hoffmann et al., 2017) but are in line with other studies that did not report a significant difference between switch and repeat trials (Meiran et al., 2011; Remijnse et al., 2013; Whitmer & Gotlib, 2012). The mixed findings in the literature could be due to the employment of slightly different paradigms, making the comparison between studies rather difficult. Moreover, this study was the first to apply a more robust statistical approach rather than rely on data aggregation (i.e., comparing mean values).

Furthermore, depressive symptoms were related to a selective and extended difficulty in performing tasks with emotional stimuli compared to non-emotional stimuli. Indeed, the participants' BDI-II scores were positively associated with longer RTs in the hot version compared to the cold version. However, this effect was not modulated by the degree of cognitive control required to perform the task, because the three-way interaction between condition, domain, and BDI-II scores was not significant. In other words, depressive symptoms were characterized by an **affective interference** not only in demanding and complex conditions but also even in simple and semiautomatic conditions (i.e., single-task blocks). These results are partly in line with the affective interference hypothesis (Siegle et al., 2002), which suggests that the automatic orienting and processing of affective stimuli interfere with attentional processing by detaining more cognitive resources in depression. Hence, longer latencies in the emotional task may be due to the distribution of cognitive resources between the completion of the task and the attentional processing of the emotional features of the stimulus, which is

slowed in individuals with greater depressive symptoms. Moreover, the reduced readiness to initiate a task under exposure to emotional stimuli compared to non-emotional stimuli may be consistent with studies that described a reduced ability to inhibit affective stimuli in individuals with depressive symptoms (e.g., Joorman & Gotlib, 2010; Joorman & Tanovic, 2014). However, the effect was not valence-specific, as no difference was found between trials that required disengagement from a previous unpleasant or pleasant stimulus. The interference of unpleasant stimuli may extend to sustained difficulty in task completion even in trials requiring disengagement from pleasant stimuli rather than selectively modulating the performance of trials requiring disengagement from unpleasant stimuli. For instance, individuals with greater depressive symptoms may have more difficulties in deactivating the unpleasant features of images, which results in poorer control over preventing irrelevant affective information from interfering with the completion of the whole emotional task (Lo & Allen, 2010). Our results are in line with one of the few studies that adopted an emotional (with pleasant and unpleasant trials) rather than a non-emotional version of the same task-switching paradigm and found a selective difficulty in the emotional task-switching paradigm, regardless of the stimulus valence, in individuals with depression (Lo & Allen, 2010). However, the authors of that study did not include the RTs for both task versions within a single statistical model but conducted two separate ANOVAs, making it impossible to compare the two task versions directly. Furthermore, contrary to our study, they did not include single-task blocks. Therefore, the previous study did not make it possible to state whether emotional material influences cognition even in relatively simple conditions or if it selectively influences high-order functions that require greater cognitive resources.

The focus on cognitive aspects of depression aligns with the Cognitive System domain within the Research Domain Criteria framework, an initiative developed to better characterize affective, cognitive, and biological factors underlying psychopathology (Insel, 2010; Kozak &

Cuthbert, 2016). The Research Domain Criteria also includes the Positive and Negative Valence Systems, domains that are related strictly to emotional processing (Keller et al., 2019). Studying how these systems interact in people with depressive symptoms is of increasing interest, and our study provides further evidence of the influence of affective stimuli on cognitive control (mixed-task blocks) and simpler attentional processing (single-task blocks). Overall, this study demonstrates that depressive symptoms are characterized by general cognitive control difficulties and the interference of affective stimuli in both complex and simple tasks.

In addition, although the order of the two tasks was counterbalanced, a control analysis revealed that the participants who first completed the emotional task had greater emotion-specific effects (i.e., greater RTs in the emotional task). In addition, those who first completed the non-emotional task had greater emotion-specific effects in the single trials compared to the task-switching trials. In this study, the inclusion of other higher order interactions, including the task order factor, was not justified. Overall, these results should be investigated further and considered in future studies.

The results of this study have not only theoretical implications but also implications for the prevention and treatment of depression. These findings suggest that reduced cognitive control abilities and an overall interference of affective stimuli might be useful in early identification of the risk for developing a full-blown depressive episode. In turn, these findings lay the foundation for the implementation of preventive programs for individuals who show difficulties in cognitive control abilities. Moreover, our findings seem compatible with the emerging evidence documenting the efficacy of cognitive control training in diminishing depressive symptoms (Koster et al., 2017). However, a combination of general and affective cognitive control training might be more effective (e.g., Iacoviello et al., 2014). To date, task-

switching training has not been employed in the treatment of depression, and future studies on both cold and hot cognitive training with this paradigm are warranted.

In interpreting our findings, several limitations should be considered. First, although the participants were given precise instructions for completing the experiment, the fact that we conducted the study remotely through a web platform, due to the COVID-19 pandemic, might have influenced the results. However, due to the ease of collecting larger samples, online studies are increasingly being conducted, and the accuracy of web platforms has been tested and validated in a recent study (Anwyl-Irvine et al., 2021). In addition, the reliability analysis conducted in this study showed the adequacy of the online assessment of the task-switching paradigm. Moreover, the fact that data collection was conducted during the second wave of the COVID-19 pandemic might limit these results to this specific context. Second, although task-switching paradigms tap distinct aspects of cognition and are considered promising tools for accurately measuring cognitive control (Meiran, 2010; Monsell, 2003), to explore cognition in people with depressive symptoms fully, future studies should consider the use of multiple tasks and employ a latent variable approach (e.g., Ambrosini et al., 2019). Additionally, although the task was extensively piloted to ensure comparability between the two task versions, they were not fully comparable. Furthermore, to make the two task versions as comparable as possible, the emotional task comprised only four emotional faces (two for gender and two for emotion). This represents a limit, because previous studies that explored emotional task-switching abilities have employed many pictures to avoid habituation (e.g., De Lissnyder et al., 2012; Grol & De Raedt, 2018). Therefore, this habituation to the emotional stimuli could have led to the absence of selective difficulties in the emotional task version as a function of depressive symptoms. Lastly, future studies should consider selecting individuals with more severe depressive symptoms to better typify the extent of cognitive control difficulties in both cold and hot contexts in depression.

In conclusion, this study provides novel evidence on the extent of cognitive control difficulties in emotional and non emotional contexts in relation to depressive symptoms. These findings show the presence of depressive symptoms is associated with a general difficulty to exert cognitive control in both contexts and with a more extended difficulty in even simple attentional processing of affective material. Future laboratory studies are warranted to confirm these findings and better understand the interplay between affect and cognition in individuals with depressive symptoms.

CHAPTER VI:

GENERAL DISCUSSION

6.1 Overview of the Aims and Findings

A promising line of research is exploring distinct domains of the Research Domain Criteria (RDoC) to better understand the mechanisms that lead to or are associated with depression and its vulnerability. The present work sought to explore affective and cognitive processes, encompassed in the Positive (PVS) and Negative Valence (NVS) and the Cognitive Systems, and their interactions in subclinical depression (dysphoria) and clinical depression. Through the study of these two conditions, it was possible to explore mechanisms related to both an at-risk condition (dysphoria) and full-blown clinical depression.

In general, Studies 1 and 2 supported the sensitivity of time-frequency analysis in reflecting multiple aspects of affective picture processing in subclinical and clinical depression. Indeed, time–frequency analysis of EEG data within specific frequency bands allows the extrapolation of information that is not available using ERPs analysis and reflects distinctive aspects of information processing (Cohen, 2014; Munneke et al., 2015). Although studies on the late positive potential (LPP) have provided important insight into our understanding of attention to salient affective cues, this measure does not fully leverage all information in the EEG signal (Morales et al., 2022). Instead, the employment of delta and theta power in Study 1 allowed us to simultaneously examine affective disposition and cognitive processing of the emotional images, respectively. For instance, delta oscillations are thought to have a functional role in monitoring the motivational relevance of affective stimuli and in the identification of pleasant/rewarding cues and are generated by subcortical regions involved in the motivational system (Foti et al., 2015; Güntekin & Başar, 2016). Instead, theta power, distributed within a large network of brain regions involved in multimodal sensory and cognitive processing

(Karakaş, 2020; Kowalczyk et al., 2013; Sauseng et al., 2010), is believed to have a role in orienting and processing arousing stimuli.

Study 1 revealed that already at the subclinical level, depression is characterized by blunted motivated attention and emotional responding to appetitive cues, as indexed by reduced LPP and delta power to pleasant images, respectively, relative to a control group. These findings suggest that depressive symptoms might relate to reduced PVS functioning and support the ***positive attenuation hypothesis*** of depression. This aligns with models describing depression as a deficit in appetitive motivation, which is related to core depressive features, such as anhedonia and behavioral apathy (Davidson, 1998; Henriques & Davidson, 2000). Indeed, additional analyses to Study 1 showed that reduced delta power to pleasant images in dysphoria was mediated by anhedonia levels, suggesting a role of anhedonia symptoms in driving reduced neural responses to appetitive cues in individuals with subclinical levels of depression. Study 1 also showed greater cognitive processing of unpleasant images, indexed by greater theta power to these stimuli relative to neutral and pleasant ones, in dysphoria but not controls. However, the greater processing of unpleasant images observed in dysphoria might not lead to greater action preparation and reactivity. Considering previous evidence on other psychophysiological indices, such as cardiac deceleration and the startle reflex (e.g., Messerotti Benvenuti et al., 2020), assessing attentional processing and motivation disposition respectively, the findings from this work are in line with the idea that depression risk might be associated with greater intake of unpleasant cues but that does not lead to greater action preparation and reactivity. Hence, the present data are not at odds with the *negative potentiation hypothesis,* which proposed that depressive symptoms are characterized by hyperarousal and motivation disposition to actively withdraw from aversive and unpleasant stimuli. However, to better clarify and explore this hypothesis and the *Emotion Context Insensitivity Hypothesis* (ECI), future studies should integrate multiple psychophysiological measures (e.g., EEG time-

frequency, cardiac deceleration, startle reflex) to concurrently tackle attentional processing and affective disposition to emotional content in depression. In terms of the RDoC matrix, Study 1 revealed an involvement of the PVS as well as an interaction between the NVS and Cognitive Systems in dysphoria.

Study 2 showed that findings on reduced electrocortical responses (LPP and delta power) to pleasant images extended from subclinical to clinical samples. Moreover, the LPP and delta power were uncorrelated and independently predicted MDD clinical status, suggesting that leveraging time- and time-frequency analyses within the same study might enhance clinical utility. Unlike Study 1, within the MDD group, there was an absence of affective modulation of delta power, namely affective elaboration of pleasant images was comparable to neutral ones. This result suggests that in clinical depression the motivational deficit might be more extended than in subclinical depression. Also, unlike Study 1, the link between time-frequency delta power and MDD status was not mediated by symptoms of anhedonia. This indicates that, in clinical phases of depression, reduced neural responses to appetitive cues might generally relate to the depressive state and are not driven by some of its specific features. This null finding could also be due to the chronicity of the disorder and the intake of psychotropic medications in the MDD group.

Taken together, Studies 1 and 2 evidenced the role of time-frequency delta power in the study of approach motivation in depressive symptoms and both supported the *positive attenuation hypothesis* in subclinical and clinical depression. In both studies, the LPP and delta power to pleasant images were reduced in dysphoria and MDD but these measures were uncorrelated, supporting the idea that they might reflect two distinct aspects of affective processing dysfunctions in depressive symptoms, namely reduced attention to salient pleasant stimuli and hypoactivation of the approach motivation, respectively. Importantly, Study 1 showed that only reduced delta power, and not the LPP, to pleasant images in dysphoria was

mediated by anhedonia levels, further supporting the selective link between time-frequency delta and approach motivation and PVS functioning. However, as suggested by the findings of Study 2, the use of the LPP and delta power as two independent measures of affective processing might improve the clinical utility, suggesting that they might be complementary.

Considering that Study 1 only tackled simple visual processing rather than higher cognitive control functioning, **Study 3** investigated how both the PVS and NVS influenced the Cognitive Systems through two versions (emotional and non-emotional) of a task-switching paradigm. What emerged from Study 3 was that depressive symptoms are characterized by overall difficulties in higher cognitive control functions but also by an affective interference of both pleasant and unpleasant cues across both lower and higher cognitive control functions. In this study, important foundations for a more precise study of cognitive processing in emotional and non-emotional contexts were set and future studies should be designed to further advance our knowledge on this matter.

Overall, these results indicate that depressive symptoms can arise from a complex interaction between distinct RDoC dimensions adding to the literature a better characterization of neural and behavioral patterns related to depressive symptoms in young adults. This offers several relevant advantages, such as the possibility of highlighting different manifestations of psychopathology pertaining to the same nosographic category (Kring & Bachorowski, 1999). Moreover, extending the study of RDoC dimensions will ultimately allow the adoption of a dimensional approach to mental disorders, whereby emotion-related disorders could be construed as deficits in the affective and cognitive dimensions of the RDoC rather than by a series of strict categorical criteria.

6.2 Clinical Implications

This line of work aims at improving the understanding of the underlying mechanisms of depression and how individuals develop depression in order to, eventually, improve the ability of clinicians to identify, prevent and/or treat the disorder.

The findings presented in this dissertation represent a step forward in the early identification of individuals that might develop depression and that might benefit from personalized types of interventions. For example, including EEG time-frequency measures of affective processing along with self-report measures during ordinary clinical screening might increase the sensitivity and specificity of identifying subclinical depressive symptoms. Then, instead of targeting individuals with subclinical levels of depression with standard protocols, it could be a useful strategy to create personalized psychology interventions based on individual subjects targeting, for example, neural responses to pleasant cues and/or cognitive control difficulties.

Regarding treatment or prevention protocols, considering that the PVS emerged as a potentially relevant domain implicated in both subclinical and clinical depression, interventions aimed at increasing approach motivation might be indicated for these conditions. For example, Positive Affect Treatment (PAT) is an intervention that comprises the planning of pleasant activities in combination with cognitive training focused on the positive, and exercises to foster pleasant experiences (Craske et al., 2016). This intervention has been shown to improve depressive symptoms relative to other interventions aimed at reducing negative affect (Craske et al., 2019). However, although the design of this protocol was based on psychophysiological and neural findings on depression such as the ones presented in this dissertation work, no study has yet explored whether PAT modulates and improves neural responses to pleasant and rewarding experiences and stimuli.

Furthermore, based on the findings on greater orienting and elaboration of unpleasant images that emerged in Study 1, two interventions could be suggested. First, training individuals with depressed mood to reduce the facilitated top-down processing of unpleasant stimuli, while increasing it for pleasant ones might be a useful strategy to diminish the tendency to automatically focus their cognitive resources on negatively valenced content, thus improving mood and psychological well-being (e.g., Dai et al., 2019; Hallion and Ruscio, 2011). Second, targeting emotion regulation by increasing the ability to use adaptive strategies, such as cognitive reappraisal, might allow individuals with depressed mood to reframe their thoughts relative to a given event or stimulus to decrease its emotional impact (Gross, 2002).

Finally, Study 3 confirmed the involvement of the Cognitive Systems functioning in depressive symptoms and this appears to be in line with the emerging evidence documenting the efficacy of cognitive control training in diminishing depressive symptoms (Koster et al., 2017). However, a combination of general and affective cognitive control training might be more effective (e.g., Iacoviello et al., 2014). To date, task-switching training has not been employed in the treatment of depression, and future studies on both cold and hot cognitive training with this paradigm could be developed.

Needless to say that more studies are warranted to refine our knowledge of specific RDoC domains implicated in at-risk conditions in order to develop more specific intervention strategies. These future efforts will guide psychophysiology and the study of mental illness toward a "precision medicine era" that will significantly improve the quality of life of the entire population.

6.3 Limitations and Future Directions

The results enclosed in this dissertation should be interpreted in light of several limitations that have partly been outlined throughout the discussions of each Study.

First, studies 1 and 3 aimed at studying at-risk individuals that are more vulnerable to developing full-blown depression. However, this work did not consider multiple at-risk conditions but only dysphoria and this significantly reduced the strength of potential inferences regarding risk factors for depression. Studying individuals that are currently free from depressive symptoms (even subclinical) but have a familiar history of depression might better disentangle whether the observed effects could be considered risk factors rather than correlates of a symptomatologic condition. In addition, the studies were cross-sectional and did not include a follow-up assessment to evaluate whether participants with dysphoria developed a depressive episode. Hence, it might be important for future research to conduct multi-wave studies on other at-risk samples (e.g., individuals with a parental history of depression, with past depression).

Second, this dissertation established that depressive symptoms are related to reduced approach motivation, cognitive control difficulties, and an affective interference of pleasant and unpleasant stimuli even in simple attentional conditions. However, this work does not fully speak to the underlying mechanisms through which these phenomena potentially interact. For instance, the study of cognitive control in emotional and non-emotional conditions (Study 3) was the first step in the exploration of the influence of PVS and NVS on cognitive functioning and was constrained to a behavioral study due to the pandemic. One hypothesis on the interaction between the PVS and the Cognitive Systems could be that the reduced sensitivity to appetitive stimuli experienced by individuals with or at risk of depressive symptoms may affect the ability to improve cognitive control abilities through the use of performance feedback (Ravizza & Delgado, 2014). Indeed, providing individuals with feedback during the execution

of a task (but also in everyday settings) usually improves their performance, whereas it does not affect individuals with depressed mood. Given the findings presented in this work on reduced approach motivation and cognitive control, future studies could implement reinforcement learning paradigms (e.g., a task-switching paradigm that includes the delivery of performance feedback) to better tackle the interaction between these two systems.

Moreover, Studies 1 and 2 assessed affective and cognitive processing with only one task, the passive viewing of emotional pictures. This task allowed studying the Initial Response to the Reward subconstruct of the RDoC, which includes the emotional responding to appetitive cues. Other tasks including different appetitive stimuli (e.g., monetary or social rewards) could be used in combination with the passive viewing to fully tackle this subconstruct in dysphoria. So far, a few initial studies have observed reduced time-frequency delta power in reward tasks (e.g., doors task) in at-risk conditions for depression (Ethridge et al., 2021; Nelson et al., 2018). However, these studies did not implement a cluster-based approach to the time-frequency analysis, thus reducing the robustness of the findings. Also, considering the growing literature on reduced ERPs to social rewards (Freeman et al., 2022) and the prominent social impairment involved in depression (Kupferberg et al., 2016), future research should explore time-frequency patterns during social/affiliative reward tasks instead of only focusing on standard monetary rewards. This would allow expanding this RDoC approach to the Systems for Social Processes functioning in the risk for depression as well as its interactions with the PVS. Finally, a more complete understanding of the mechanisms underlying the PVS might be granted by the implementation of multiple tasks assessing other subconstructs of the RDoC (e.g., Effort expended to obtain reward, and Reinforcement Learning).

Additionally, the emotion-cognition interaction could be further explored through the integration of multiple psychophysiological measures. For example, a peculiar measure in this

regard is the startle eyeblink reflex, which consists of the rapid evoked contraction of the orbicularis oculi muscle. When a non-startling stimulus (prepulse) is presented immediately before (less than 500 ms) a startle-eliciting stimulus (probe), the amplitude of the startle reflex is attenuated, a phenomenon known as "prepulse inhibition" (Graham, 1992). The amplitude of reflex inhibition indicates the level of attentional resources allocated to the prepulse, namely the greater the allocation to the prepulse, the greater the inhibition of the startle reflex (Bradley et al., 1993). Instead, when the startle probe is presented during affective processing more than 500 ms after the beginning of the presentation of an emotional stimulus, the startle amplitude reflects affective modulation. Specifically, the reflex is potentiated during unpleasant affective states and inhibited during pleasant affective states (e.g., Bradley et al., 1999; Dichter et al., 2002). The literature on the attentional and affective modulation of the startle in clinical depression suggests that this condition is related to a general insensitivity to emotional stimuli (Boecker & Pauli, 2019). However, studies on depression risk are still very mixed and remain largely unexplored. For instance, regarding affective modulation, studies reported reduced startle potentiation to unpleasant stimuli in individuals with dysphoria (Messerotti Benvenuti et al., 2020), but also enhance startle potentiation in individuals with past depression (Vaidyanathan et al., 2014).

Another caveat is that Study 2 used slightly different demographic groups relative to the other two studies. Study 1 and 3 included young adults (mean age = 20.5 and 25.4, respectively) living in Padova (Italy), while Study 2 included adults (mean age = 38.7) from the Tallahassee community in the USA. However, the fact that Study 2 confirmed findings from Study 1 mean that, even across different socio-cultural and demographic characteristics, reduced approach motivation is a robust finding in individuals with depressive symptoms. Also, most of the participants across all three studies were Caucasian and future studies should include more diverse samples.

Although this was not the focus of the present dissertation, many environmental factors may act as catalysts for vulnerability factors in determining the development of depression and future studies should take this into account (Weinberg, Kujawa, & Riesel, 2022). For example, exposure to negative stressful life events is a well-established risk factor for psychopathology and seems to have an impact on multiple domains. Chronic stress has significant adverse effects on brain regions implicated in reward processing (Burani, Gallyer, et al., 2021; Pizzagalli, 2014) and endocrine and autonomic regulation (Shet et al., 2017). Of note, there is evidence of how stressful life events interact with neural activity to rewards to prospectively predict the development of depression (Burani, Klawohn, et al., 2021), further supporting the role of an environmental influence on the functioning of an RDoC domain in determining vulnerability for psychopathology.

6.4 Conclusions

Taken together, findings described in this dissertation are relevant in the advancement of the dimensional characterization of mechanisms underlying depression and its risk. This work supports the notion that reduced approach motivation might be the driving force associated with the manifestation of subclinical (Study 1) and clinical levels of depression (Study 2), instead of imbalances of the withdrawal motivational system. Also, subclinical depression appears to be characterized by greater orienting and processing of unpleasant stimuli (Study 1) as well as cognitive control difficulties, especially in affective conditions (Study 3). Ultimately, the evaluation of these measures might be leveraged to improve clinical utility and design more precise identification and personalized intervention protocols.

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