**UNIVERSITY OF PADOVA**

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Final dissertation

# Affective processing in anhedonia: An ERP study

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## Table of Contents

## ABSTRACT

**Background:** Anhedonia, defined as a loss of pleasure towards appetitive stimuli, is a core symptom of depression and a vulnerability factor for its development. Prior research has demonstrated that anhedonia is associated with blunted emotional processing of appetitive stimuli. However, the precise relationship between the different stages of affective processing and anhedonia remains poorly understood. Event-related potentials (ERPs) offer a valuable tool for differentiating between distinct temporal stages of affective processing. Specifically, the Cue-P300 reflects cue-evaluation and allocation of attentional resources toward the expected emotional stimulus, the Stimulus Preceding Negativity (SPN) indicates affective anticipation, and the Late Positive Potential (LPP) represents motivated attention and elaboration of affective stimuli.

**Aim of the study:** The objective of the present study was to disentangle the influence of anhedonia on the distinct stages of affective processing through the analysis of the ERP components Cue-P300, SPN and LPP.

**Materials and methods:** Forty-five university students (31 females) with varying anhedonia levels, as assessed through the Snaith-Hamilton Pleasure Scale (SHAPS), and no current diagnosis of depression participated in the study. Participants underwent an S1-S2 paradigm, in which an image (S2) was preceded by a cue (S1) anticipating its valence (pleasant, neutral, unpleasant). The electroencephalography (EEG) was recorded to obtain ERPs related to the processes of interest (Cue-P300, SPN, and LPP). Linear mixed-effects models were used for statistical analysis, with a separate model computed for each ERP component of interest

**Results:** The analyses yielded a significant main effect of Category for the SPN and LPP, which was further qualified by a significant Category × SHAPS interaction effect showing that higher anhedonia levels were associated with larger SPN and smaller LPP amplitudes specifically in response to pleasant images as compared to neutral ones. The Cue-P300 analysis revealed a significant main effect of Category, with a larger Cue-P300 amplitude for pleasant images compared to both neutral and unpleasant images. No significant Category × SHAPS interaction effect was found for the Cue-P300.

**Conclusion:** These findings suggest a complex pattern of affective processing in non-clinical individuals with anhedonia, characterized by a rapid transition from increased anticipation to reduced elaboration of appetitive stimuli. Therefore, the present study elucidates how anhedonia

influences the different stages of affective processing, further exploring the affective processing deficits linked to depression vulnerability.

**Keywords:** Anhedonia, ERPs, Emotion, Affect

# FIRST PART

# CHAPTER ONE: DEPRESSION VULNERABILITY: INSIGHTS FROM THE RDoC FRAMEWORK

## 1.1 Depression: clinical overview and epidemiology

Understanding the clinical complexity of major depressive disorder (MDD), a serious and heterogeneous mood disorder, requires a close examination of its core symptoms and diagnostic criteria. Depressive symptoms include persistent depressed mood, diminished interest in pleasurable activities or anhedonia, changes in appetite or weight, sleep disturbances, lack of energy or fatigue, psychomotor retardation or agitation, feeling of worthlessness or excessive guilt, poor concentration, and suicidal ideation (American Psychiatric Association, 2015). According to the Diagnostic and Statistical Manual of Mental Disorders, 5$^{th}$ edition (DSM-5, American Psychiatric Association, 2015) a diagnosis of MDD can be reached if the individual presents at least five of the aforementioned symptoms nearly every day for a minimum duration of 2 weeks (American Psychiatric Association, 2015). Importantly, the MDD diagnosis necessitates the presence of depressed mood or anhedonia, resulting in significant distress or functional impairment (American Psychiatric Association, 2015). The multifaceted nature of MDD in the DSM-5 results in substantial diagnostic heterogeneity, allowing for up to 227 possible symptom combinations that can meet the criteria for an MDD diagnosis (Park et al., 2017). Although debated, the DSM-5 includes a range of MDD specifiers such as melancholic, atypical, anxious distress, and psychotic features, that aim to capture the heterogeneity of symptom presentations in depression (American Psychiatric Association, 2015; Wu et al., 2022). This clinical diversity implies that MDD may not arise from a single pathway, but rather from multiple interacting risk factors including genetic, neurobiological, psychological, and environmental, that

manifest in distinct symptom profiles across individuals (Jokela et al., 2019). Moreover, MDD is highly comorbid with other mental disorders including panic disorders, substance-related disorders, anorexia nervosa, bulimia nervosa, and obsessive-compulsive disorder (American Psychiatric Association, 2015).

Recent epidemiological surveys estimate over 320 million cases of MDD worldwide, making it one of the most prevalent and burdensome forms of psychopathology today (Kessler & Bromet, 2013; World Health Organization, 2017). In 2015, the World Health Organization reported that 4.4% of the global population suffered from depression, marking an 18.4% increase since 2005 (World Health Organization, 2017). The lifetime prevalence of MDD is estimated to be much higher, impacting nearly one in six adults (Bromet et al., 2011). Despite the known variability in lifetime prevalence estimates, these statistics suggest that about 20% of the adult population meet the MDD diagnostic criteria at some point in their lives (Bromet et al., 2011). Moreover, the World Health Organization survey found that the 12-month prevalence of depression was comparable across high-, medium-, and low-income countries, indicating that MDD is a global condition affecting societies at all economic levels (Otte et al., 2016). Notably, depression prevalence varies by age and gender, peaking in older adults and affecting females at rates that are nearly twofold higher than males (World Health Organization, 2017) (Figure 1.1). The average age of onset for depression is estimated to be around 15 years, with earlier depression onsets being more commonly observed in women (Lewinsohn et al., 1994). Furthermore, the mean age of onset, gender ratio, and symptom profile of depression were found to be similar across different cultures and countries (Kessler & Bromet, 2013).

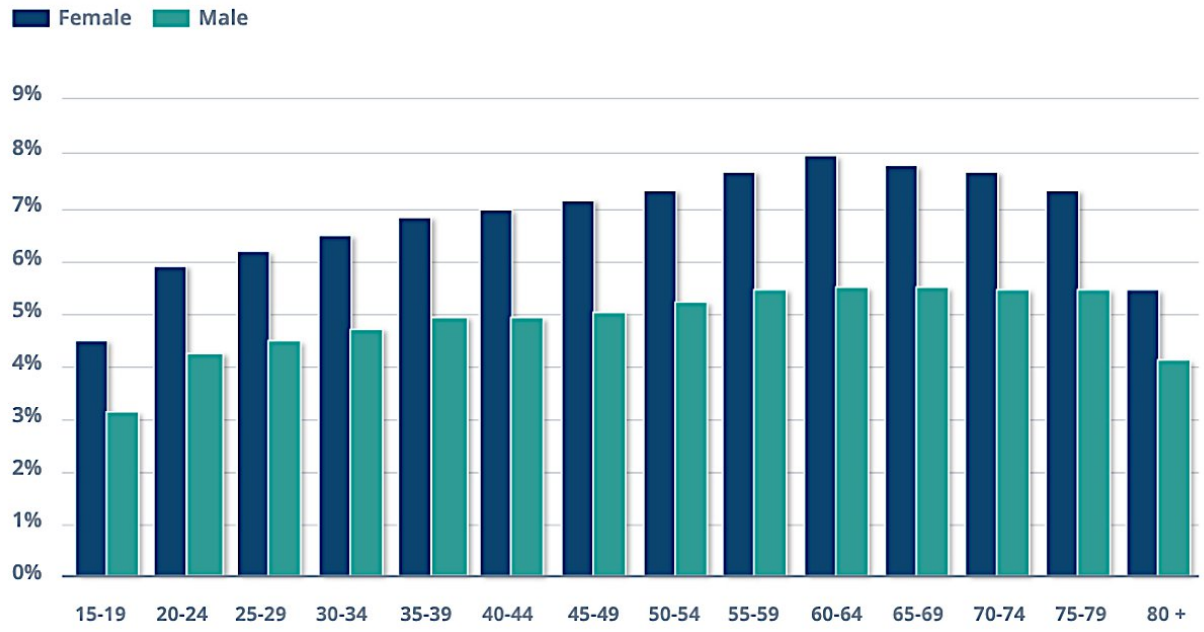


**Figure 1.1** Global Depression Prevalence by Age and Sex (%), with Age-Standardized Estimates. The representation was based on data from the Global Burden of Disease Study 2015 (World Health Organization, 2017).

The rising prevalence of MDD, coupled with its significant impact on daily functioning, has made it one of the leading causes of disability globally (Lawrence et al., 2010; World Health Organization, 2017). The pervasive nature of depression imposes a substantial burden on a patient (Briley & Lépine, 2011). Specifically, MDD was found to increase mortality risk by 60-80% in both those with and without specific medical illnesses (Cuijpers et al., 2014). Most alarmingly, individuals diagnosed with depression face dramatically increased suicide risks, with females approximately 20 times and males 27 times more likely to take their own lives; notably, this risk is even higher among youth, estimated at 30 times greater (Briley & Lépine, 2011; Liu et al., 2024). MDD also imposes a significant economic toll on individuals, their families, and society at large, stemming from both lost work productivity and the treatment costs (Wang et al., 2003). The risk of recurrence after a first major depressive episode is estimated at 50%, increasing with each subsequent episode (Hardeveld et al., 2013). Indeed, the number of previous episodes is one of the

strongest predictors of MDD recurrence (Hardeveld et al., 2010). The 15-year recurrence rate for MDD is estimated to be 35% in the general population, rising to 85% among those in specialized mental healthcare settings (Hardeveld et al., 2010). Additionally, the progression of depression in adults appears to be a little less promising as age increases when compared to younger patients (Penninx et al., 2011). Unfortunately, residual symptoms and functional impairments frequently persist even after the remission of MDD, underscoring the enduring and significant burden of depression (Ormel et al., 2004). The chronic nature of depression significantly diminishes both the quality and length of life, as demonstrated by MDD accounting for approximately 37% of mental disorder-related disability-adjusted life years (DALYs) in 2019 (Liu et al., 2024). Longitudinal studies report that MDD diagnosis enhances the risk of other debilitating disorders including diabetes mellitus, obesity, stroke, heart disease, hypertension, and even cognitive impairment (Penninx et al., 2013). Indeed, patients with depression were found to have a higher risk of cardiac mortality after an initial myocardial infarction (Briley & Lépine, 2011).

The high prevalence and chronic nature of depression, coupled with its significant psychological and economic burden, result in substantial functional impairments that exert considerable pressure and strain on the individuals affected by this disorder and the society as a whole. For this reason, significant efforts have been dedicated to developing effective treatments, including pharmacological (e.g., selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)), psychological (e.g., cognitive behavioral therapy), and neuroscientific interventions (e.g., vagus nerve stimulation, transcranial magnetic stimulation) (Ceskova & Silhan, 2018; Dimidjian et al., 2011; Duval et al., 2006; Oates et al., 1991; Trambaiolli et al., 2021). Although many MDD treatments have demonstrated some effectiveness in reducing depressive symptoms, a substantial number of individuals either do not respond to those

interventions or experience high rates of recurrence (Baghai et al., 2006; Fava & Davidson, 1996; Mauskopf et al., 2009). Indeed, MDD remission rates have been estimated at 45% over a 2-year period, with patients experiencing moderate to severe depression reporting even lower rates of remission (McIntyre, 2004). As a result, recent efforts have shifted towards MDD prevention through the identification of early-onset indicators and vulnerability markers for depression (Moretta & Messerotti Benvenuti, 2022; Walker et al., 2014). Monitoring individuals who are at an elevated risk for depression has been shown to be an effective method for preventing its development (Dell'Acqua et al., 2023). Early identification of MDD has been shown to enhance the effectiveness of rapid interventions and treatment strategies (Zhang et al., 2023). Current findings, though preliminary, offer promising evidence that early interventions may help reduce depressive symptoms and lower the incidence of a full-blown MDD diagnosis (Clarke et al., 2001; Hansen et al., 2012; Walker et al., 2014).

Although the precise etiology of MDD remains unclear, recent advances point to the interplay of multiple pathological mechanisms contributing to its development (Cui et al., 2024). Several hypotheses have been proposed to explain the pathogenesis of MDD, including biological, psychological and environmental factors at play (Remes et al., 2021). However, none of these mechanisms alone can fully explain the complexity of MDD; instead, each may serve as a risk factor that increases the likelihood of developing depression (Otte et al., 2016).

**Biological risk factors** of MDD encompass physical health conditions, genetics, dysregulated hypothalamic-pituitary-adrenal (HPA) axis, inflammation as well as functional brain abnormalities. Individuals diagnosed with medical conditions, including but not limited to HIV/AIDS, anemia, hypertension, osteoporosis, or cancer were found to have a higher risk of developing MDD (Sigvardsen et al., 2025). Moreover, MDD has been suggested to have a

heritability rate of 30-50% (Kendall et al., 2021), and first-degree relatives of individuals with MDD have a lifetime risk of approximately 35% of developing the disorder (Geschwind & Flint, 2015). Moreover, MDD has been suggested to have a heritability rate of 30-50% (Kendall et al., 2021), and first-degree relatives of individuals with MDD have a lifetime risk of approximately 35% of developing the disorder (Geschwind & Flint, 2015). Given the polygenic nature of MDD, current genome-wide association studies (GWAS) focus on identifying multiple genetic variants that contribute to depression risk (Hyman, 2014). Specifically, two genetic factors implicated in depression are the brain-derived neurotrophic factor (BDNF) gene and single nucleotide polymorphisms (SNPs) within candidate genes (Remes et al., 2021). Another biomarker of depression is the dysfunction of the HPA axis, a key part of the neuroendocrine system responsible for regulating body's stress response (Jesulola et al., 2018; Lima-Ojeda et al., 2018). Notably, many depressive symptoms such as mood, appetite or sleep disturbances reflect hypothalamic dysfunction (Guerry & Hastings, 2011). The hyperreactivity of the HPA axis, due to impaired negative feedback, leads to persistently elevated cortisol levels, contributing to those depressive symptoms as well as the abnormal pattern of stress responding in depression (Guerry & Hastings, 2011). While not the sole pathway, heightened cortisol levels can also negatively impact brain structures (e.g., the amygdala, hippocampus), impair emotion regulation, suppresses neurogenesis, and may contribute to inflammation, adding onto the depression risk (Herbert, 2013). To date, abnormal HPA axis in individuals with depression has been one of the most robust and consistent biological risk factors in depression (Ehlert et al., 2001). Indeed, research shows that at least 50% of individuals with depression show dysregulated HPA axis function (Nestler et al., 2002). Elevated inflammation, marked by increased levels of pro-inflammatory cytokines, may also contribute to the development of depression (Remes et al., 2021). A meta-analysis found

significantly higher levels of interleukin-6 (IL-6) in individuals with depression (Howren et al., 2009). Moreover, inflammation may affect MDD progression, as elevated tumor necrosis factor-alpha (TNF-α) has been observed in patients with recurrent episodes (Moylan et al., 2013). Functional brain abnormalities have been suggested as another potential biomarker of depression, with particular focus on fronto-limbic dysregulation in MDD (Zajkowska et al., 2021). Neuroimaging studies support the presence of amygdala hyperactivation alongside prefrontal cortex hypoactivation in response to emotional stimuli, observed both in individuals with MDD (Jaworska et al., 2015) and those at increased risk for depression (Zhong et al., 2011).

**Psychological factors** such as attributional style, personality traits and cognitive biases have been consistently linked to the onset and maintenance of depressive symptoms. Abramson, Metalsky, and Alloy's (1989) hopelessness theory of depression postulates that a negative attributional style—tendency to explain negative events through stable and global causes—increases vulnerability to developing "hopelessness depression", mainly characterized by apathy, low energy, and motor retardation (Joiner, 2001). This model is supported by a substantial body of research consistently linking internal, stable, and global attributions for negative events to depressive symptoms (Joiner, 2001; Raps et al., 1982; Sweeney et al., 1986). Additionally, although less strongly, attributing positive events to external factors such as luck has also been associated with depression (Sweeney et al., 1986). More recent research has also identified socially prescribed perfectionism as a significant predictor of MDD, suggesting that individuals with high external expectations may be more vulnerable to depression (Malinowski et al., 2017). Moreover, heightened Behavioral Inhibition System (BIS) activity—within Gray's Reinforcement Sensitivity Theory, reflecting increased sensitivity to punishment and avoidance tendencies—has been found to positively predict depressive symptoms (Takahashi et al., 2021). In the domain of cognitive

biases, studies have found that individuals with MDD often exhibit negative attentional biases and a tendency to sustain negative affect over time (Murrough et al., 2011). This aligns with Beck's cognitive triad theory, which highlights three core negative thought patterns in depression: a pessimistic view of the self, the world, and the future (Beck, 1979). Supporting this theory, empirical studies have found a strong correlation ($r = 0.65$) between the cognitive triad and depressive symptoms in adults (Beck & Perkins, 2001). Similar positive associations have also been observed in children and adolescents experiencing depressive symptoms (Berghuis et al., 2020; Braet et al., 2015). Additionally, the tendency toward catastrophizing and a negative interpretation bias was found to be more pronounced in individuals with depression compared to healthy controls (Nieto et al., 2020). Higher levels of rumination, characterized by "repetitive thought patterns focused on the causes and consequences of one's negative feelings" (Nolen-Hoeksema et al., 2008), also plays a significant role in development, persistence and recurrence of depressive symptoms (Nolen-Hoeksema et al., 2008; J. M. Smith & Alloy, 2009). In particular, rumination along with reduced vagal control of the heart, an index of autonomic flexibility, have been associated with MDD, highlighting the interaction between cognitive and physiological dysregulation in depression (Carnevali et al., 2018; Moretta & Messerotti Benvenuti, 2022).

**Environmental factors** such as stressful events (e.g., loss of employment, health problems, financial insecurity) have also been shown to contribute to increased depression risk, particularly in the year leading up to MDD onset (Kessler, 1997). Indeed, patients with MDD report on average higher frequency of stressful life events as compared to the general population (Gómez Maquet et al., 2020; Gunilla Olsson, 1999). A prominent line of research has delved into adverse childhood experiences—such as physical and sexual abuse, psychological neglect, and exposure to domestic violence—as significant precursors to depression in later life (Cheong et al.,

2017; Kendler et al., 2004; Rousson et al., 2020). The literature underscores a solid connection between childhood maltreatment and elevated depression risk (Afifi et al., 2014; Li et al., 2016). In fact, children from abusive households show a higher probability of experiencing depressive symptoms compared to those from non-abusive families (Toth et al., 1992). Additionally, an authoritarian parenting style marked by demanding, obedience-oriented but not responsive behavior, was positively associated with depressive symptoms among adolescents (Sharma et al., 2011). Moreover, studies indicate that children of parents diagnosed with depression tend to experience a significantly earlier onset of MDD compared to those without a family history of the disorder (Weissman, 1987). This heightened vulnerability may reflect an interplay of biological, psychological, and environmental factors, where genetic predisposition, parental cognitive biases as well as authoritarian parenting style all contribute to increased depression risk. Social relationships, or more precisely lack thereof, is another factor in depression vulnerability. A longitudinal study found that individuals experiencing social strain, poor relationship quality, or lack of social support were all at a higher risk to develop depression (Teo et al., 2013). Lastly, socioeconomic status (SES) also appears be at plays with significantly higher depression prevalence observed among those with a low SES (Freeman et al., 2016). The recognition of vulnerability factors is valuable for the early identification of depression risk as well as the design of preventive interventions and novel treatment approaches (Cui et al., 2024).

### 1.2 Anhedonia: a feature and a vulnerability factor for depression

Anhedonia, characterized by a diminished ability or complete inability to experience pleasure in typically pleasurable activities, is one of the core features of depression (American Psychiatric Association, 2015; Gorwood, 2008). Since the publication of the Feighner Criteria in

1972 and continuing through the DSM-5, anhedonia has been consistently recognized as a core symptom of depression (Feighner, 1972; Treadway & Zald, 2011). In the DSM-5, anhedonia is one of the two key symptoms necessary for the formal MDD diagnosis and a primary feature of a melancholic specifiers of the MDD (American Psychiatric Association, 2015). Anhedonia frequently presents alongside other clinical symptoms like apathy, fatigue, and avolition, thereby leading to significant overlap in their clinical manifestations (Kieslich et al., 2022). The prevalence of clinical anhedonia is estimated to be around 70% among those individuals diagnosed with MDD (Cao et al., 2019). Moreover, anhedonia symptoms often persist in MDD remission, with approximately one-quarter of individuals in remission experiencing significant anhedonic symptoms despite being classified within a non-clinical range of depression (Di Nicola et al., 2013).

In addition to being a core symptom of depression, anhedonia is also associated with poor clinical outcomes in MDD, impacting both the progression of the disorder and the effectiveness of treatment interventions (Myerson, 1946; Pelizza & Ferrari, 2009). A plethora of evidence suggests an association between anhedonia and a more severe and pervasive depression course (Whitton & Pizzagalli, 2022). Gabbay and colleagues (2015) found that the severity of anhedonia is closely associated with increased depression severity in adolescents, including both the frequency and duration of MDD episodes. Another study demonstrates that severe anhedonia heightens the risk of depressive symptoms persisting 12 months after an initial MDD diagnosis (Spijker et al., 2001). Moreover, anhedonia being a risk factor for increased suicidal ideation might be clinically useful in the identification of MDD patients that require more intensive clinical attention and interventions (Ducasse et al., 2021; Whitton & Pizzagalli, 2022). The presence of severe anhedonia in MDD patients has also been linked to worse treatment response to various

types of antidepressant interventions including pharmacological options (Dunlop et al., 2020), cognitive behavioral therapy (Craske et al., 2016), as well as repetitive transcranial magnetic stimulation (Downar et al., 2014). Notably, elevated pre-treatment anhedonia levels have been identified as a unique negative predictor of longer remission times and fewer depression-free days following treatment with SSRIs (McMakin et al., 2012).

The clinical presentation of anhedonia is thought to stem from impaired reward processing at the neurobiological level (Höflich et al., 2019). However, reward processing, and thus anhedonia, is not a unitary construct but rather an umbrella term encompassing a range of different processes (Berridge & Kringelbach, 2008; Höflich et al., 2019). The task of unraveling the basis of anhedonia has become even more complex with the shift from defining anhedonia as simply an "inability to feel pleasure" to a broader concept of "loss of interest or pleasure", which adds a motivational dimension to its understanding (Kieslich et al., 2022). Pleasure and the motivation to experience it rely on separate neurocognitive mechanisms, which can be selectively compromised in various patients, underscoring the importance of targeted treatment strategies (Husain & Roiser, 2018; Treadway & Zald, 2011). To advance this effort, it is essential to examine the cognitive and neural processes that contribute to anhedonia (Kieslich et al., 2022). In that attempt, some authors (Admon & Pizzagalli, 2015; Rømer Thomsen et al., 2015) conceptualize anhedonia in terms of three partially distinct subtypes of reward processing: reward wanting, reward liking, and reward learning, each associated with dissociable neural pathways. Reward wanting corresponds to the motivational drive to obtain the reward, rewards liking refers to the hedonic pleasure derived from rewards, and reward learning involves using past reward experiences to guide future behaviors (Berridge & Robinson, 2003; Rømer Thomsen et al., 2015). Impairments in any of the three subtypes of reward processing can lead to behavioral deficits, thereby contributing to anhedonia

manifestation (Berridge & Robinson, 2003; Rømer Thomsen, 2015). Recently, a more comprehensive model of anhedonia has been put forward, in which reward processing encompasses various cognitive operations where reward-related information influences and shapes behavior (Kieslich et al., 2022). Husain and Roiser (2018) explain that before acting, individuals generate various behavioral options, which are evaluated through a cost-benefit analysis in order to determine the most advantageous choice based on the perceived reward value. After option selection but before action initiation, the body experiences physiological changes associated with motivational arousal in anticipation of the forthcoming reward (Husain & Roiser, 2018). Subsequently, motor and premotor mechanisms are engaged, as part of the appetitive or approach phase of behavior, to initiate an action necessary to obtain the reward (Husain & Roiser, 2018; Kieslich et al., 2022). The following interaction with behavioral goals constitutes the consummatory phase of reward processing which leads to a hedonic response also known as pleasure (Husain & Roiser, 2018; Kieslich et al., 2022). Lastly, learning based on the previous reward outcomes feedbacks to the option selection stage for better future cost-benefit decisions (Fig. 1.2) (Husain & Roiser, 2018). Depending on which specific components of reward processing are disrupted and how they alter the overall balance of the reward system, such impairments can give rise to distinct subtypes of anhedonia, which manifest across various mental disorders (Rømer Thomsen et al., 2015). For instance, individuals with MDD frequently report a reduced capacity to experience pleasure, indicating diminished activity in at least one reward processing component, whereas drug addiction is marked by heightened activity in different reward components, manifesting as excessive reward wanting (Rømer Thomsen, 2015). Thus, both heightened and diminished dysfunctional activity in specific components of the reward processing system can have pathological consequences (Rømer Thomsen, 2015). Moreover, evidence suggests that the

various facets of reward processing may be associated with partially independent neural pathways (Der-Avakian & Markou, 2012). The study of the specific alterations in individual components of reward processing could not only elucidate the observed heterogeneity of anhedonia but also facilitate the development of targeted treatments (Kieslich et al., 2022; Rizvi et al., 2016).

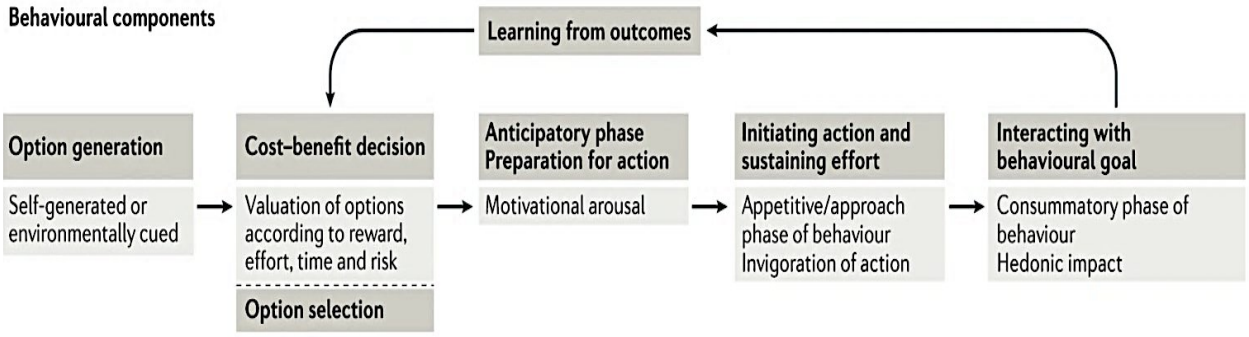


**Figure 1.2** Components of reward processing. Adapted from Husain and Roiser (2018).

Current literature provides compelling evidence for the investigation of the distinct reward processing components, in that reward anticipation, through a variety of techniques including neuroimaging, physiological responses, as well as behavioral tasks (Kieslich et al., 2022). However, to date, the diminished experience of pleasure in anhedonia is most frequently assessed through self-report questionnaires (Gorwood, 2008). Among the available measurement tools are the Chapman's Physical Anhedonia Scale (PAS; Chapman et al., 1976), the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) and the more recent Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015). These self-report measures demonstrate good validity, with individuals with depression consistently reporting reduced pleasure experience when compared to healthy individuals (Watson & Naragon-Gainey, 2010).

Beyond anhedonia's well-established role as a core symptom of MDD, it has also been described as a process that might underlie vulnerability to depression (Pelizza & Ferrari, 2009). Precisely, the deficit in hedonic response is viewed as an inherent predisposition that increases the likelihood of developing depression (Pelizza & Ferrari, 2009). Paul Meehl (1987) introduced the concept of "hedonic capacity", suggesting that it exists on a spectrum, in that some individuals possess a greater natural ability to experience pleasure, while others have a lower capacity. In this view, individuals with lower hedonic capacity are said to be more susceptible to developing depression (Meehl, 1987).

The study of anhedonia in the context of depression vulnerability is crucial not only because it serves as an early indicator of the onset of MDD but also due to its positive association with the number, frequency, and severity of depressive episodes. Additionally, anhedonia also impacts the treatment course of MDD, increasing the probability of recurrence and poorer responsiveness to a range of interventions (Craske et al., 2016; Downar et al., 2014; Dunlop et al., 2020; Whitton & Pizzagalli, 2022). These findings highlight the importance of early depression diagnosis and prevention approaches, which can be accomplished through investigating vulnerability factors such as anhedonia (Dell'Acqua et al., 2023; Winer et al., 2016).

### 1.3 The Research Domain Criteria (RDoC): a framework to study depression vulnerability

Recent breakthroughs in clinical psychology, psychophysiology, neuroscience, and genetics have provided significant new insights into the underlying mechanisms, treatment options, and prevention of numerous mental disorders (Hyman, 2007). However, these findings often do not align with the widely used nosographic classification systems like the DSM-5 or International Classification of Diseases (ICD), which base their diagnosis on the strict symptom

number and frequency and whether they lead to significant distress or functional impairment (Hyman, 2007; Insel et al., 2010). Additionally, these categorical measures require the presence of at least 5 symptoms for a diagnosis while not accounting for the different symptom combinations and those with fewer symptoms (i.e. subclinical) (Hyman, 2007; Insel et al., 2010). These rigid classification boundaries, coupled with a lack of emphasis on the underlying mechanisms of dysfunction, fail to capture the multidimensionality and complexity of heterogeneous mental disorders, among which depression (Insel et al., 2010; Regier et al., 2009). Additionally, the overlap in phenomenology across the diagnostic categories hinders accurate prediction of treatment responses (Insel et al., 2010). As a result, the development of early-onset prevention and intervention approaches targeting the underlying pathophysiological mechanisms has been delayed (Cuthbert, 2020; Insel et al., 2010).

In an effort to bridge the translational gap between neuroscience research and clinical practice, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) project in 2009 (Cuthbert & Insel, 2013). The RDoC offers new opportunities to classify mental disorders and the underlying mechanisms, based on an understanding of the various dysfunctions in psychological and biological systems (Böttger et al., 2023; Cuthbert, 2014). The project marks a significant shift toward a pathophysiology-based framework, prioritizing research on the functional dimensions of behavioral, cognitive, and affective processes, spanning from normal to abnormal (Cuthbert, 2014; Cuthbert & Insel, 2013; Morris et al., 2015). The RDoC model is structured as a matrix, featuring six fundamental domains of functioning arranged in rows: Positive Valence Systems, Negative Valence Systems, Cognitive Systems, Social Processes, Arousal and Regulatory Systems, and Sensorimotor Systems (Böttger et al., 2023; Insel et al., 2010). Each of these domains can be further analyzed across different units, organized in columns:

genes, molecules, cells, circuits, physiology, behavior, and self-report (Insel et al., 2010). Additionally, the six fundamental domains are divided into constructs and subconstructs (Cuthbert, 2014). Mental disorders are also examined along the two additional key dimensions of the RDoC matrix: neurodevelopmental trajectories and environmental influences (Fig 1.3; Cuthbert, 2014). The RDoC framework enforces the idea of integrating multiple levels of analysis across its various dimensions, deepening our understanding of vulnerability to psychopathology (Dillon et al., 2014). This leads to a broader understanding of RDoC dimensions and constructs, recognizing them not only as outcomes of psychopathology but also as markers of heightened vulnerability to mental disorders (Dell'Acqua et al., 2023). To build on this understanding, further research on at-risk groups is crucial to explore how specific dysfunctions in RDoC constructs are associated with the development of psychopathology (Dell'Acqua et al., 2023).

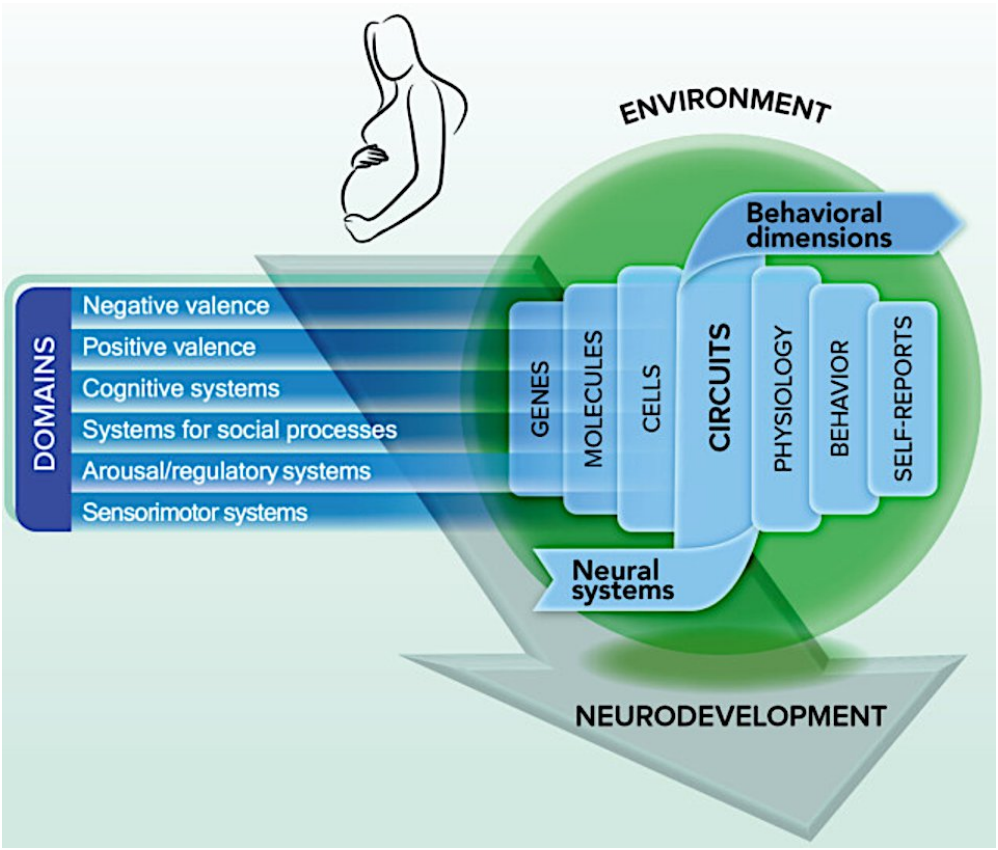


**Figure 1.3** Diagram of the RDoC framework. Adapted from Cuthbert (2020).

The RDoC initiative is based on the premise that the fundamental domains serve as root mechanisms of mental disorders, thereby helping to clarify their underlying etiology and vulnerability (MacNeill et al., 2021; Shankman & Gorka, 2015). Instead of simply outlining the characteristics of mental disorders, such as MDD, RDoC constructs offer insights into how these conditions develop and, importantly, identify the individuals at risk (Dell'Acqua et al., 2023; Shankman & Gorka, 2015). The matrix's high explanatory power represents a significant advantage of the RDoC project in informing future research directions and interventions for mental health (Shankman & Gorka, 2015). Psychophysiology is one of the key research disciplines contributing significantly to the refinement of the RDoC framework for various psychopathologies (Kujawa & Burkhouse, 2017). In fact, psychophysiology research can inform RDoC domains across multiple levels of analysis, ranging from neural and autonomic (i.e., physiological) level to behavioral and self-report levels (Kujawa & Burkhouse, 2017).

### 1.3.1 The Positive Valence Systems: anticipating and elaborating affective stimuli

Among the RDoC constructs, the Positive Valence Systems (PVS) may be of particular interest to the study of anhedonia in the context of depression vulnerability. The PVS functional domain encompasses all the responses and actions related to motivation, pleasure, and reward (Hill et al., 2023; Morris & Cuthbert, 2012). Evidence of reduced functioning in the Positive Valence Systems (PVS) domain has been observed in individuals with depression across various units of analysis, including self-reports (McFarland & Klein, 2009; Treadway & Zald, 2011), behavioral data (Treadway et al., 2012), electrophysiological measures (Proudfit et al., 2015), and brain imaging data (Pizzagalli, 2014). Indeed, findings from functional magnetic resonance imaging (fMRI) studies indicate reduced activation to rewarding stimuli in subcortical areas in

MDD patients, particularly in regions involved in reward processing, such as the ventral striatum (Ng et al., 2019).

Within the PVS domain, three primary constructs can be identified: reward responsiveness, reward learning, and reward valuation (National Institute of Mental Health, 2020). Each of these constructs comprises several subconstructs, among which those related to anticipating, obtaining, elaborating, and responding to pleasant or rewarding stimuli (see Fig.1.3.1) (National Institute of Mental Health, 2020; Olino, 2016). The aforementioned facets of reward, though interrelated, are distinguishable through a variety of techniques, ranging from behavioral assessments to neural imaging (Wang et al., 2022). Reward anticipation occurs in the time leading up to reward delivery, allowing individuals to prepare for the upcoming events (Der-Avakian et al., 2015). Neurophysiological studies allow for the measurement of neural activity during the period preceding a reward cue or a delay in receiving a reward (Wang et al., 2022). In the case of the latter, behavioral paradigms such as the Monetary Incentive Delay (MID) task, along with its adaptation, the Social Incentive Delay (SID) task, are particularly effective at disentangling the anticipation phase of reward processing (Knutson et al., 2000; Oldham et al., 2018). To respond effectively to pleasant or rewarding stimuli, it is essential to engage with and process the affective stimuli (Wang et al., 2022). A growing consensus is that reward anticipation activates the ventral striatum (including the NAcc), whereas the receipt and consumption of rewards is linked to increased activation in ventromedial prefrontal cortex regions (Knutson et al., 2001; Kohls et al., 2013; Liu et al., 2011).

| Construct | Subconstruct |
|---|---|
| Reward Responsiveness | Reward Anticipation |
| | Initial Response to Reward |
| | Reward Satiation |
| Reward Learning | Probabilistic and Reinforcement Learning |
| | Reward Prediction Error |
| | Habit |
| Reward Valuation | Reward (probability) |
| | Delay |
| | Effort |

**Figure 1.3.1** The constructs and subconstructs within the Positive Valence System (PVS) of the RDoC initiative. Adapted from National Institute of Mental Health (2020).

Previous research in both preclinical and clinical populations indicates diminished appetitive anticipation and elaboration in individuals diagnosed with depression (McFarland & Klein, 2009; Rizvi et al., 2016; H. Wu et al., 2017), as well as in children with a familial risk for the disorder (Kujawa et al., 2014). Furthermore, the diminished anticipation and elaboration of rewards have been suggested to predict the onset of depression (Bress et al., 2013; Nelson et al., 2016a). Findings by Sherdell et al. (2012) on MDD patients revealed lower levels of reward anticipation and diminished motivation to put in effort to attain rewards as compared to healthy controls. Despite the increasing body of research, it remains unclear whether vulnerability to depression arises from a functional deficit at a specific stage of reward processing, highlighting the need for further exploration (Rømer Thomsen et al., 2015).

Examining the anticipation and elaboration of affective stimuli is fundamental as dysfunctions at these stages may play a crucial role in the emergence and maintenance of anhedonia and MDD. Specifically, blunted anticipation of positive events may weaken reward responsiveness and motivation, contributing to depression (Olino et al., 2014; Sherdell et al., 2012). In other words, reduced seeking of rewards along with experiencing lower positive affect

when rewards are obtained, can progressively lead to an overall reduction in responses to these rewards (Olino et al., 2014). In turn, disruptions in stimulus processing, such as diminished processing of pleasant stimuli, may further exacerbate depression, leading to a worse prognosis in terms of psychological, physical and social functioning deficits (Wong et al., 2024).

# CHAPTER TWO: EVENT-RELATED POTENTIALS (ERPs) IN THE STUDY OF EMOTIONAL PROCESSES

## 2.1 The dimensional model of emotion

Emotions can be understood as dispositions towards actions, facilitating survival in a rich, complex and dynamic environment (Lang et al., 1998). In this regard, emotions emerge alongside physiological preparations for action even when such action are not performed (Lang et al., 1998). Lang and colleagues (1998) proposed a dimensional model of emotions, conceptualizing it as an interaction of three partially independent reactive systems: cognitive, physiological and motoric (Hugdahl, 1981). The cognitive system relates to a subjective experience of a stimulus, the physiological system encompasses somato-visceral and central nervous responses to the stimulus, and motoric system involves a series of expressive motor changes as well as actions towards the stimulus (Hugdahl, 1981; Lang et al., 1998). Each of these systems gives rise to a different facet of emotional expression – verbal reports, physiological changes and behavioral responses – thereby illuminating interindividual differences in affective disposition (Lang et al., 1998).

Different emotional states can be characterized along the two dimensions of human emotions: valence and arousal (Lang et al., 1997b). The valence dimension discriminates stimuli based on their pleasantness or unpleasantness, guiding actions along the approach/withdrawal axis (Lang et al., 1997b). The arousal dimension reflects the subjective feeling of activation or calmness to the stimuli and determines the intensity of physiological responses (Lang et al., 1997b). Within this framework, Lang and colleagues (1997) devised a depository of visual stimuli known as International Affective Picture System (IAPS). The IAPS database is composed of over 1100 pictures, each with specific arousal and valence ratings (Figure 2.1), making them universally applicable in various experimental settings (Bradley & Lang, 2017).

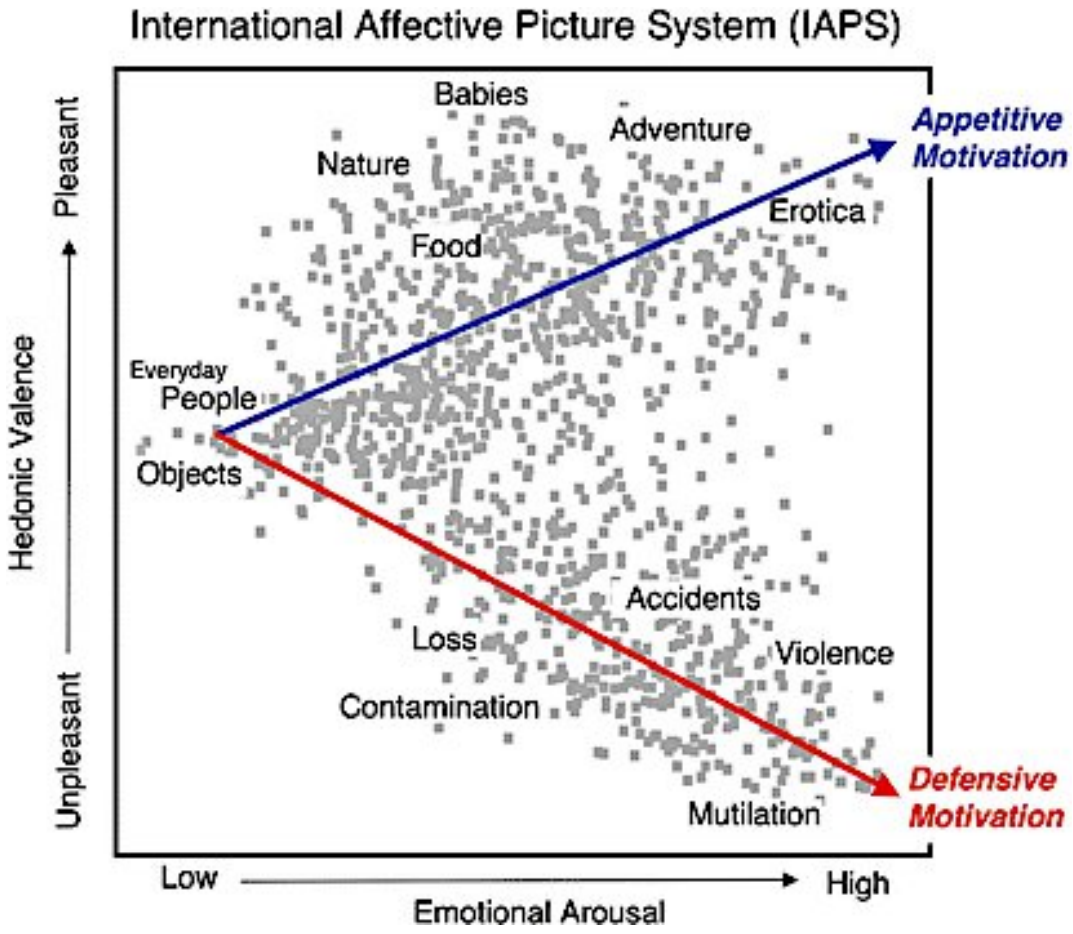


**Figure 2.1** Pictures from the International Affective Picture System (IAPS) distributed along the two-dimensional space composed of hedonic valence (pleasant/unpleasant) and emotional arousal (high/low). Each square in the plot represents ratings for a single picture. Adapted from Bradley and Lang (2017).

## 2.2 Event-related potentials (ERPs) in the study of emotional processing

### 2.2.1 ERPs and the electroencephalographic signal

The electroencephalogram (EEG) is a widely used neurophysiological measurement technique applied in both clinical and scientific settings. From the first recording of human electrical activity in 1929 till now, significant advancements have expanded the use of EEG in studying emotional processing and the neural mechanisms underlying affective states (Keil, 2013; Luck, 2014). The EEG captures the spontaneous and continuous electrical activity of thousands,

or even millions, of neurons in the brain, recorded at the scalp using surface electrodes (Keil, 2013). Specifically, the EEG signal represents summation of electrical potentials generated in the extracellular fluid of postsynaptic neurons. The excitation of the postsynaptic neuron leads to a flow of electrical current generating regions of opposing positive and negative charges separated by distance, also known as a dipole (Buzsáki et al., 2012). The dipole of a single neuron is far too small to be reliably detected at the scalp electrode. Instead, the EEG signal reflects the summed activity of numerous individual dipoles in the brain (Buzsáki et al., 2012). For a measurable, non-zero signal to emerge, these neural dipoles must be both co-aligned and co-activated (Buzsáki et al., 2012; Luck, 2014). If neuronal alignment is random, no clear dipole will form, while dipoles in opposite directions will cancel each other out, eliminating any detectable signal (Cohen, 2014; Luck, 2014).

Brain activity is inherently rhythmic. The EEG allows to capture those neural oscillations which are characterized by synchronized changes in the excitability of groups of neurons (Cohen, 2014). Neural oscillations can be classified into bands based on their frequency, amplitude, and morphology, and may occur independently or in relation to discrete events. The frequency of a rhythm represents the number of cycles per second, measured in hertz (Hz), while its amplitude reflects the wave's size, quantified in microvolts (μV; Cohen, 2017). Frequency and amplitude share an inverse relationship, when one increases, the other typically decreases (Buzsáki, 2011).

The EEG activity can be either spontaneous, occurring in the absence of discrete events, or related to specific internal or external stimuli (Cohen, 2014). The event-related EEG segments (i.e., time-locked to the presentation of a stimulus), extracted from the overall EEG signal through averaging, are called event-related potentials (ERPs). Averaging activity across multiple trials, reduces the random noise in the EEG signal, allowing for the clear identification of ERPs (Figure

2.2; Keil, 2013). The number of trials required for averaging depends on the ERP component of interest, but in general, a higher trial count enhances signal quality by reducing random noise more effectively (Luck, 2014). A common approach to classifying ERPs relies on their polarity, latency, and scalp topography (Luck & Kappenman, 2013). Polarity reflects the direction of voltage deflection – positive (P) or negative (N), latency indicates the time between stimulus onset and the component's peak and scalp topography pinpoints where the component is most prominent (frontal, central, parietal, occipital, or temporal regions; Luck & Kappenman, 2013). To illustrate, the P100 is an ERP component characterized by a positive deflection occurring approximately 100 ms after stimulus onset, most prominent over occipital sites. Alternatively to the latency-based classification, ERP components can also be labeled based on their ordinal position within the waveform, such as P1 for the first positive peak, or by their functional meaning, as seen with the mismatch negativity (MMN) for detection of sensory mismatch (Luck, 2014). The amplitude of an ERP component generally reflects the strength of neural activation; however, its interpretation depends largely on the context of the experimental paradigm (Keil, 2013).

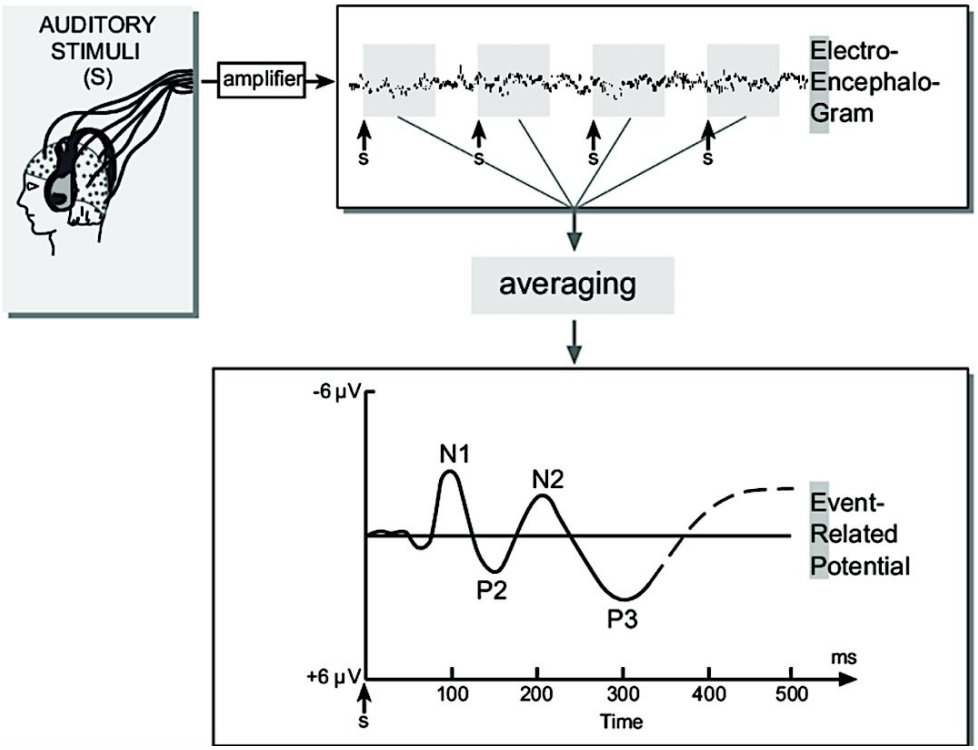


**Figure 2.2** Illustration of ERP extraction from EEG data in response to repeated auditory stimuli (S). The top left section shows EEG recording during auditory stimulus presentation, followed by signal amplification. The top center displays raw EEG segments time-locked to stimulus onset, marked by arrows. These are then averaged across trials to produce the ERP waveform (bottom section), revealing distinct components (e.g., N1, P2, N2, P3) plotted over time. Adapted from Hasting (2008).

### 2.2.2 Event-related potentials (ERPs) in the study of emotions

In recent decades, investigations into emotional processing have gained increasing attention, shifting focus away from the traditional reliance on subjective emotional states (LaBar & Cabeza, 2006; LeDoux, 2000). One particularly valuable method for exploring the temporal dynamics of affective events is the use of ERPs, prized for their high temporal precision and accuracy (Mueller et al., 2017). Unlike fMRI, which approximates neural events on a second-by-second basis, ERPs offer millisecond-level resolution, capturing the brain's electrical activity at the cortex (Cohen, 2014). This direct measurement, in contrast to fMRI's reliance on blood oxygen level-dependent (BOLD) signals, provides a more immediate window into the unfolding of the emotional processes

(Cohen, 2014; Luck & Kappenman, 2013). In laboratory ERP settings, researchers often employ paradigms involving affective stimuli (such as pictures, faces, or scenarios) systematically varying in valence (the degree of pleasantness or unpleasantness) and arousal (the intensity of emotion), enabling a comprehensive assessment of emotional processing (Cuthbert et al., 2000; Dell'Acqua et al., 2024; Moretta & Messerotti Benvenuti, 2023; Mueller et al., 2017). The influence of both valence and arousal extends across both early sensory and later cognitive ERP components, highlighting their modulation of multiple stages of information processing (Olofsson et al., 2008; Palomba et al., 1997). Although valence and arousal are at least partially independent, highly pleasant or unpleasant stimuli are often rated also as more arousing (Lang, 1995). This is vital to consider when interpreting affective responses to stimuli as they may be influenced by both valence and arousal dimensions.

The affective modulation of late ERP components, occurring around 200-300 ms post-stimulus onset, has been extensively studied in the literature (Olofsson et al., 2008). However, growing evidence suggests that emotional processing (i.e. emotional elaboration of stimuli) may also influence neural activity at the early stages of perceptual processing (Batty & Taylor, 2003; Carretié et al., 2004; Foti et al., 2009, 2010). Some studies report an enhanced P1 amplitude in response to emotional images, likely reflecting heightened early attentional allocation and processing in the visual cortex (Delplanque et al., 2004; Mueller et al., 2009). Negative valence stimuli, in particular, have been found to elicit larger P1 amplitudes compared to pleasant and neutral ones, indicating a heightened sensitivity of the processing system to unpleasant stimuli (Carretié et al., 2004; Smith et al., 2003). Yet, findings on the modulation of early sensory ERP components by affective context remain inconsistent, with other research indicating a reduction in P1 amplitude for emotional stimuli (Rigoulot et al., 2008). Additionally, affective modulation of

P1 appears to be more consistent in the context of facial stimuli: indeed, Foti et al. (2010) observed a greater P1 deflection to fearful faces compared to neutral ones in a passive emotional picture reviewing task. Another early sensory ERP component sensitive to the emotional content of stimuli is the N1, a negative centroparietal deflection peaking around between 100 and 200 ms (Luck & Kappenman, 2013). Notably, studies have reported larger N1 amplitudes for both pleasant and unpleasant images compared to neutral ones, suggesting a heightened early-stage visual processing of emotionally salient content (Foti et al., 2009; Keil et al., 2001). Although some studies have reported reduced habituation of N1 responses to high-arousal unpleasant stimuli (Carretié et al., 2003), subsequent research has failed to replicate these findings consistently (Olofsson & Polich, 2007). Nevertheless, the broader evidence on affective modulation of early ERP components indicates that emotionally valenced stimuli, particularly unpleasant ones, tend to elicit stronger neural responses, suggesting an early attentional prioritization toward negative stimuli (Olofsson et al., 2008).

Middle-latency components, primarily linked to stimulus discrimination and response selection, display a more pronounced affective modulation, particularly in terms of arousal, than early ERP components (Di Russo et al., 2006; Olofsson et al., 2008). One such component, the Early Posterior Negativity (EPN), emerges within the 150–300 ms range and is highly sensitive to emotional arousal (Luck & Kappenman, 2013; Olofsson et al., 2008). Highly arousing images, whether pleasant or unpleasant, elicit stronger EPN amplitudes compared to low-arousal stimuli (Schupp et al., 2003). This affective modulation likely reflects an increased allocation of selective attention toward arousing stimuli, thereby facilitating their further processing due to their intrinsic relevance (Schupp et al., 2004; Schupp et al., 2003).

Late ERP components, emerging > 300 ms after stimulus presentation, are associated with higher-order cognitive processes such as resource allocation, saliency detection, and working memory updating (Luck, 2014). Among these endogenous components, the P3 family of components is particularly sensitive to factors such as target probability, arousal, and motivational significance (Duncan-Johnson & Donchin, 1977; Olofsson et al., 2008). Numerous studies have demonstrated that P300 is modulated by emotional content, with both pleasant and unpleasant stimuli eliciting larger amplitudes (Luck & Kappenman, 2013; Palomba et al., 1997). This effect, thought to reflect enhanced attentional allocation driven by motivational salience has been observed not only for affective images but also for emotional adjectives, faces, and emotionally conditioned cues, further emphasizing the relevance of this component in the study of emotional processing (Allison, 1999; Begleiter et al., 1979; Luck & Kappenman, 2013). Another key ERP component in affective research is the Late Positive Potential (LPP), a prolonged positivity that extends beyond the P300 latency (Luck, 2014). A more detailed examination of the LPP and its implications for emotional processing will be explored in the later section (2.3.3).

## 2.3 Distinct phases of emotional processing: anticipation and elaboration

Identifying specific stages of appetitive stimulus processing can not only provide valuable insight into the fundamental components of emotional processing but importantly serve as a marker for vulnerabilities to depression, such as anhedonia (Davidson et al., 2003). This can be accomplished using objective neuroscientific techniques. While fMRI's high spatial resolution precisely localizes neural activation, its poor temporal resolution can blur the fast-paced dynamics of reward processing, potentially merging neural signals that are temporally adjacent yet reflect distinct psychological processes (e.g., anticipation versus elaboration; Wang et al., 2020). This

challenge can be addressed by analyzing ERPs from EEG data, which offer the fine temporal resolution needed to disentangle these successive phases of appetitive processing (Glazer et al., 2018). A widely used paradigm in ERP affective research to achieve this is the S1-S2 task. In this design, an initial cue stimulus (S1, or warning stimulus) signals the emotional valence of the upcoming target stimulus (S2, or imperative stimulus), with a fixed inter-stimulus interval (ISI) separating the two (Buodo et al., 2012; Poli et al., 2007; Walter et al., 1964). This two-stimulus task provides a valuable framework for disentangling distinct phases of emotional processing, namely, anticipation and elaboration, by allowing for the examination of multiple ERP components associated with these processes (Buodo et al., 2012; Novak & Foti, 2015). Examining several ERP components involved in the appetitive processing allows for the disentanglement of the different phases of emotional processing (i.e. anticipation and elaboration), by indexing each phase with a temporally and functionally distinct ERP component (Glazer et al., 2018). Such a multicomponent ERP analysis holds significant value in emotion processing research, as it enables the isolation of relevant neural activity from temporally overlapping signals, resulting in clearer and more cohesive interpretations of findings (Glazer et al., 2018).

### 2.3.1 Cue-P300 and Stimulus preceding negativity: emotional anticipation

The two primary ERP components associated with emotional anticipation are the Cue-P300 and Stimulus Preceding Negativity (SPN). Both electrophysiological markers can be reliably elicited using the S1-S2 paradigm, measured at their respective latencies (Buodo et al., 2012; Poli et al., 2007). The Cue-P300 is a positive deflection over parietal regions, peaking around 300 ms after the onset of the cue (S1) stimulus (Novak & Foti, 2015; Thompson et al., 2023). Within this context, the Cue-P300 amplitude reflects affective engagement, essentially, the degree of

attentional allocation toward the upcoming salient stimulus (Novak & Foti, 2015). Studies using the MID paradigm have shown that monetary incentives enhance Cue-P300 responses, with larger amplitudes observed in emotional (potential win or loss) trials compared to neutral ones (Figure 2.3) (Novak & Foti, 2015; Thompson et al., 2023). However, evidence for Cue-P300 emotional modulation in S1-S2 paradigms is mixed, with some studies reporting no significant differences between emotional and neutral cues in healthy controls (Buodo et al., 2012; Poli et al., 2007). These inconsistencies highlight the need for further research into affective engagement, both in healthy individuals and in those with mood disorder symptoms such as anhedonia.

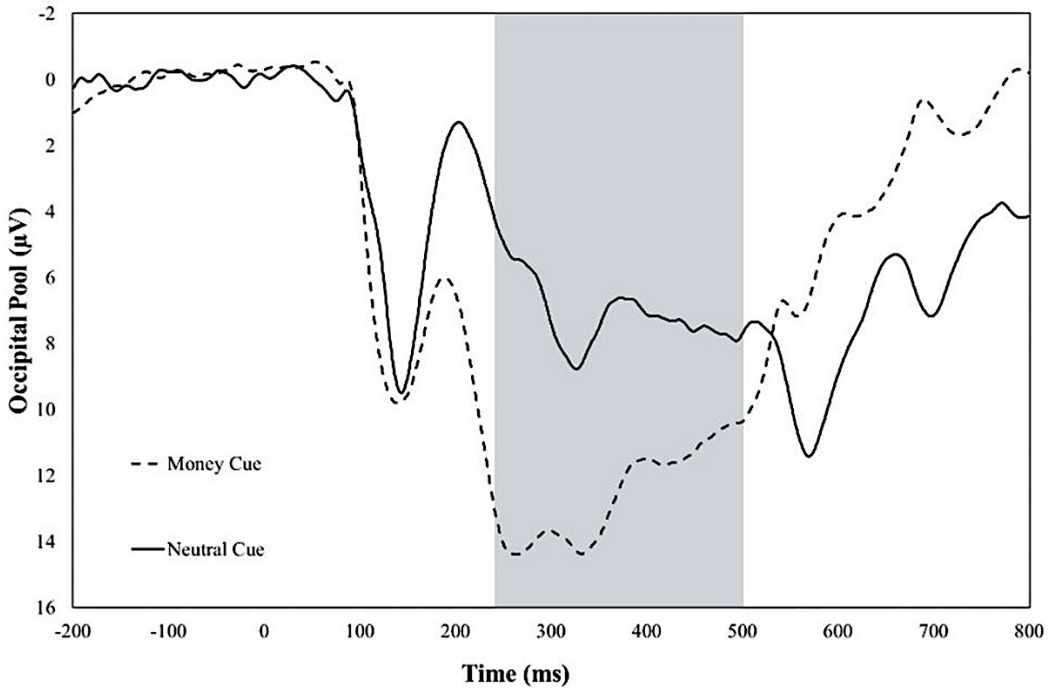


**Figure 2.3** ERP waveforms (pooled: Oz, O1, O2) during monetary incentive delay (MID) task. The money and neutral cue were presented at 0 ms, and the Cue-P300 was scored as the mean amplitude in the 250-500 ms time window (shaded region). The mean Cue-P300 amplitude was larger for monetary compared to neutral cues. Adapted from Thompson et al. (2023).

Another ERP associated with anticipatory processes is the Stimulus Preceding Negativity (SPN), a slow negative potential peaking at fronto-central sites approximately 200 ms before the

onset of the target stimulus (S2) and that reflects affective anticipation (Luck & Kappenman, 2013; Poli et al., 2007). The SPN is considered a non-motor counterpart of the Contingent Negative Variation (CNV) (Brunia, 1988). While the CNV reflects both anticipatory processing and motor readiness, the SPN specifically indexes expectancy-related neural activity in the absence of a required response, thus capturing the purely cognitive aspects of anticipation (Brunia, 1988; Walter et al., 1964). Studies employing visual emotional stimuli as S2 in the S1-S2 task consistently report greater SPN amplitude, a more negative deflection, when participants anticipate emotional (pleasant or unpleasant) images compared to neutral ones (Amrhein et al., 2005; Klorman & Ryan, 1980; Simons et al., 1979). This pattern aligns with findings from monetary reward and punishment paradigms, where SPN amplitudes are larger (more negative) for anticipation of gains or losses relative to neutral conditions (Figure 2.4) (Böcker et al., 2001; Kotani et al., 2001, 2003; Thompson et al., 2023). However, picture-viewing tasks may offer a more refined approach to studying emotional anticipation, as they allow for precise manipulation of emotional dimensions such as valence and arousal, thereby eliciting distinct affective states (Lang et al., 1993; Poli et al., 2007). Notably, research has demonstrated that SPN amplitude is particularly enhanced when anticipating stimuli with higher arousal levels, further reinforcing its role in processing emotionally salient cues (Poli et al., 2007; Takeuchi et al., 2005). Taken together, these findings suggest that the SPN is an important neural marker of anticipation sensitive to both the valence and arousal of affective stimuli and influenced by the degree of motivational engagement with the upcoming stimulus (Brunia et al., 2011).

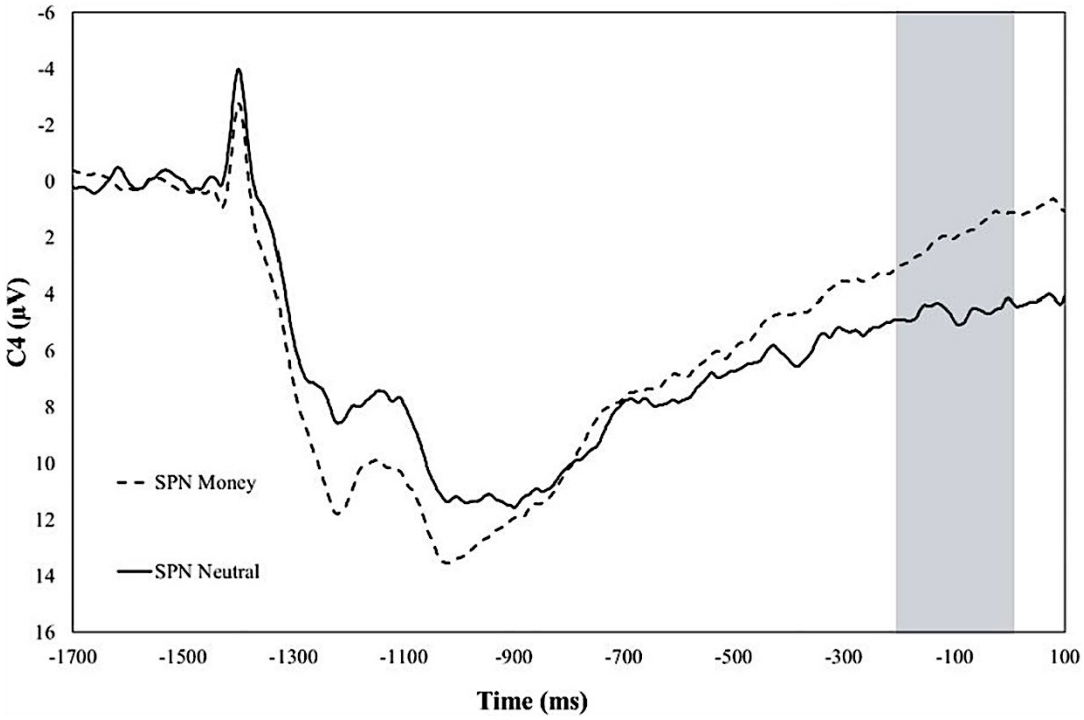


**Figure 2.4** ERP waveforms at C4 during monetary incentive delay (MID) task. The money and neutral feedback were presented at 0 ms, and the SPN was scored as the mean amplitude in the -200-0 ms time window (shaded region). The mean SPN amplitude was larger for monetary compared to neutral feedback. Adapted from Thompson et al. (2023).

### 2.3.2 Late positive potential: emotional processing

The Late Positive Potential (LPP) is an ERP linked to later, more elaborate stages of emotional processing. The LPP appears as a sustained positive deflection over centroparietal regions, typically emerging around 300 ms after the target (S2) stimulus (Luck & Kappenman, 2013). This late positive potential is primarily linked to the allocation of motivated attention and cognitive resources recruitment for the evaluation of emotionally salient stimuli (Lang & Bradley, 2010). The LPP holds particular significance in affective processing research, as it reflects motivated attention driven by the activation of appetitive or defensive motivational systems (Lang & Bradley, 2010). Consistent findings indicate that emotional stimuli elicit a larger LPP amplitude compared to neutral ones (Figure 2.5) (Hajcak & Foti, 2020), highlighting its role in signaling the

engagement of the appetitive motivational system (Cuthbert et al., 2000; Hajcak & Foti, 2020; Moretta & Messerotti Benvenuti, 2023). The amplitude of the LPP has been shown to scale with stimulus arousal, with larger LPP responses elicited by high-arousal emotional stimuli, regardless of valence, compared to neutral ones (Cuthbert et al., 2000; Palomba et al., 1997; Schupp & Kirmse, 2021). While LPP's early phase partially overlaps with the P300 component, the later portion (> 600 ms) is more specifically tied to motivated attention towards the stimulus and elaboration of its emotional meaning (De Cesarei & Codispoti, 2006). Notably, the LPP serves as a robust and stable marker of affective processing, demonstrating consistency over time and resistance to variations in stimulus duration and size (Codispoti et al., 2007; De Cesarei & Codispoti, 2006).

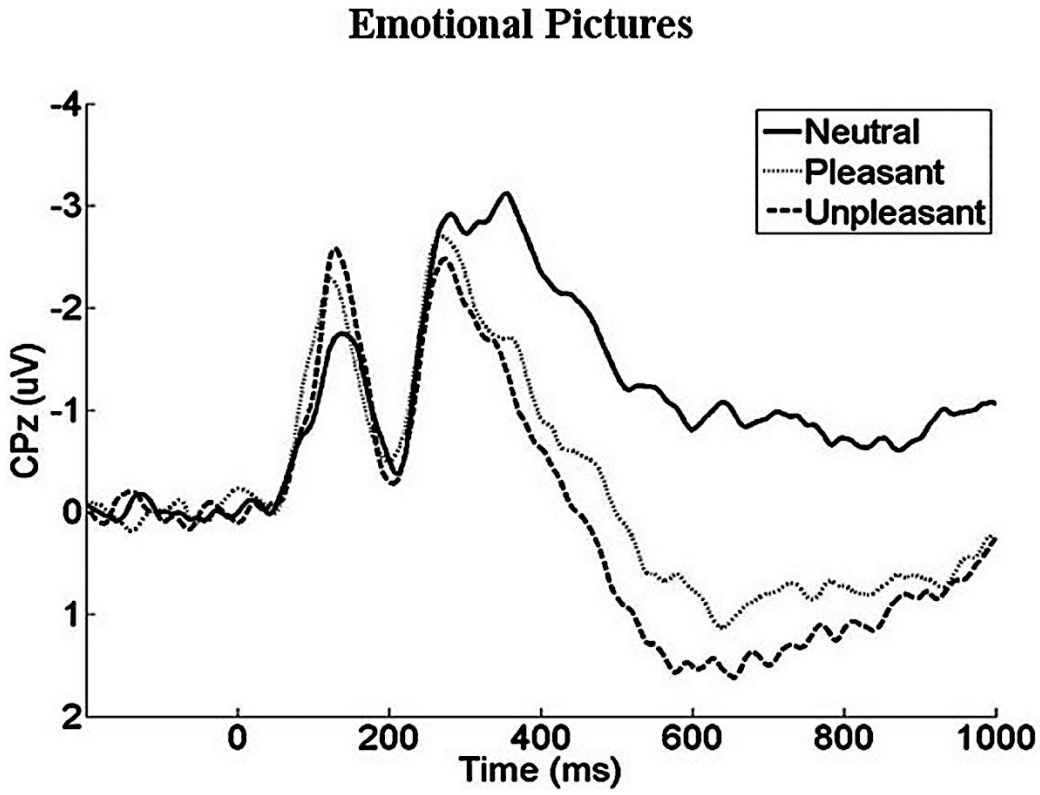


**Figure 2.5** ERP waveforms at CPz during passive viewing of neutral, pleasant, and unpleasant pictures. Picture presentation occurred at 0 ms, and the LPP emerged starting around 300 ms after picture onset with larger amplitude for affective pictures (pleasant and unpleasant) compared to neutral ones. Adapted from Hajcak and Foti (2020).

## 2.4 ERPs of emotional processing in depression and anhedonia

In the context of depression and anhedonia, examining ERP components as electrophysiological indices of emotional responding stages can offer valuable insight into the underlying processing deficits. A substantial body of research supports the association between depression and a reduced elaboration of affective (both pleasant and unpleasant) stimuli, as reflected by reduced LPP (Grunewald et al., 2019; Proudfit et al., 2015). Notably, individuals diagnosed with depression (Foti et al., 2010; MacNamara et al., 2016; Weinberg et al., 2017) and at-risk individuals without a formal diagnosis (Kujawa et al., 2012) consistently exhibit attenuated LPP responses to unpleasant but not neutral stimuli when compared to healthy controls. Complementarily, a blunted response to positively valenced stimuli, evidenced by a diminished LPP amplitude to pleasant as compared to neutral stimuli, has been found in individuals with full-blown clinical depression (Figure 2.2; Dell'Acqua et al., 2022; Proudfit et al., 2015; Weinberg et al., 2016). This pattern extends to at-risk individuals without a formal diagnosis, who similarly show attenuated LPP amplitudes in response to pleasant stimuli when compared to healthy controls (Kujawa et al., 2012; Moretta & Messerotti Benvenuti, 2023; Nelson et al., 2015). Remarkably, this blunted response to pleasant stimuli has been identified as a predictor of depression onset (Nelson et al., 2016; Sandre et al., 2019), suggesting that impaired elaboration of appetitive emotional content may serve as a vulnerability indicator for the disorder. This aligns closely with the nature of anhedonia, reinforcing the notion that diminished capacity to engage with appetitive experiences is a key feature in depression (Klawohn, Burani, et al., 2021). This is supported by findings of reduced Cue-P300 (Thompson et al., 2023; White et al., 2021), SPN (Ren et al., 2024), and LPP (Dell'Acqua et al., 2022; Kujawa & Burkhouse, 2017; Moretta & Messerotti Benvenuti, 2023) amplitudes to pleasant or rewarding stimuli in individuals with depression and those at risk.

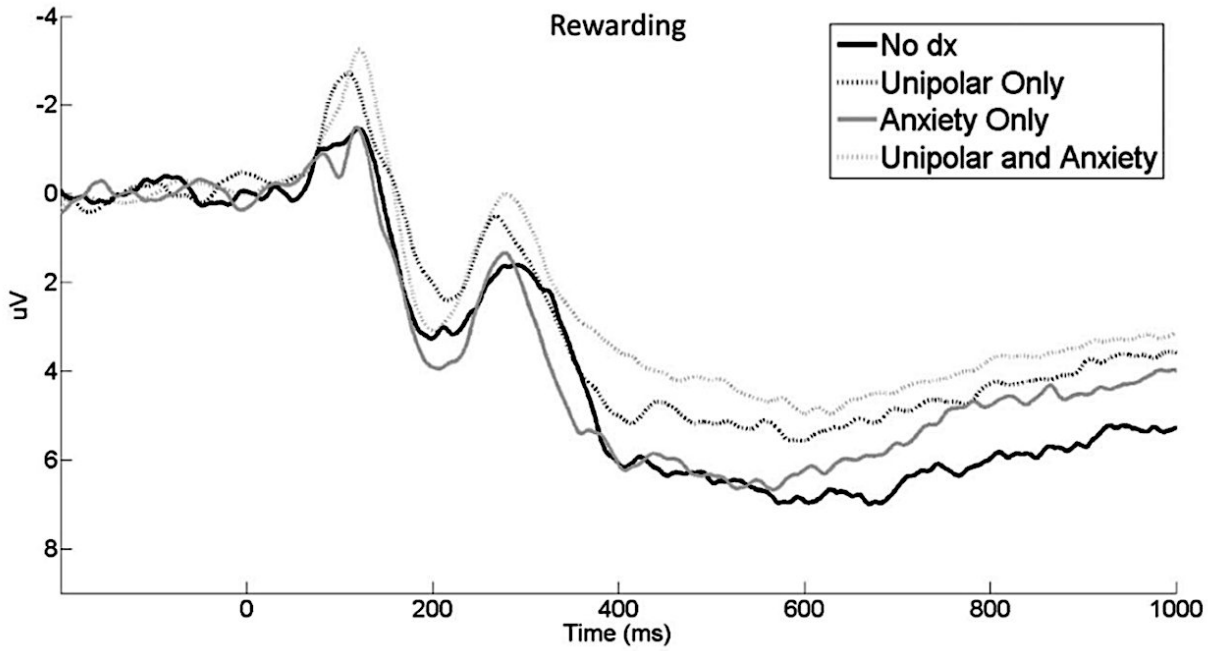


**Figure 2.6** ERP waveforms (pooled: Pz, Cz, CP1, CP2) during IAPS picture viewing paradigm in individuals with no current or past diagnosis (No dx), a current diagnosis of anxiety only, a current diagnosis, of a unipolar depressive disorder only, and a current diagnosis of both anxiety and a unipolar depressive disorder. Current depression diagnosis was associated with a blunted LPP (400-1000 ms) to rewarding pictures compared to controls. Adapted from Weinberg et al. (2016).

However, it remains unclear which processes might be specifically associated with anhedonia, namely whether anhedonia is characterized solely by reduced elaboration or also by diminished anticipation of emotional stimuli. Although limited, studies employing the MID task have reported reduced Cue-P300 amplitudes for gain versus neutral feedback in individuals with clinical depression, a pattern not observed in healthy controls (Thompson et al., 2023; White et al., 2021). In addition, a study examining temporal dynamics of incentive processing in anhedonia using a cued gambling task found that the anhedonia group with low anticipation scores had a blunted Cue-P300 response to gain compared to neutral context (Chen et al., 2018). These findings suggest that anhedonia may be linked to a diminished early affective engagement with anticipated rewards.

The current findings on SPN in altered emotional processing remain inconclusive in depression and those at risk. These discrepancies may stem from the SPN's sensitivity to various experimental manipulations or the differences in task designs across studies (Kotani et al., 2001; Poli et al., 2007). For instance, some studies employing the MID task have reported attenuated SPN amplitudes in response to rewards among individuals with diagnosed depression compared to healthy controls (Ren et al., 2022, 2024; Sun et al., 2023). Conversely, research by Umemoto and Holroyd (2017) found the opposite pattern of heightened SPN responses to rewards in college students exhibiting depressive symptoms compared to controls. In their probabilistic reinforcement task, they observed an increased SPN amplitudes, in both depressed and non-depressed individuals, when reward probability decreased suggesting SPN to be sensitive to improbable positive events (i.e. probable negative outcomes) in depression (Umemoto & Holroyd, 2017). Notably, this effect was more pronounced in depressed individuals compared to healthy controls, suggesting a pattern of possible pessimistic outlook on future reward delivery and a general bias towards negative stimuli in depression (Umemoto & Holroyd, 2017). Adding to the complexity, other studies suggest no significant modulation of SPN in anticipation of appetitive stimuli in depression (Chen et al., 2018; Thompson et al., 2023). These conflicting findings underscore the need for a more in-depth investigation of Cue-P300, SPN, and LPP components as potential indicators of anticipation and elaboration deficits in anhedonia, an early vulnerability to depression.

# SECOND PART

# CHAPTER THREE: THE STUDY

## 3.1 Introduction and hypotheses

In the preceding chapters, the core symptomatic profile and epidemiology of MDD have been outlined. To reiterate, depression ranks among the most widespread mental disorders globally, imposing a profound psychological, physical, and economic toll, not only on the affected individuals but on the society as a whole (Kessler & Bromet, 2013; World Health Organization, 2017). The growing urgency to improve treatment and prevention strategies has fueled extensive research into the vulnerability markers underlying MDD. Among these, anhedonia—a diminished ability to experience pleasure and emotional disengagement from rewarding stimuli—has emerged as a key factor in depression, extending beyond its role as a symptom (American Psychiatric Association, 2015; Pelizza & Ferrari, 2009). More specifically, anhedonia has been recognized as a potential endophenotype of MDD, contributing to both its onset and progression (Pizzagalli, 2014). Yet, anhedonia is not a single, uniform construct and recognizing its heterogeneity could offer deeper understanding of depression vulnerability (Treadway, 2015).

The Research Domain Criteria (RDoC) launched by the National Institute of Mental Health (NIMH) goes beyond the "categorical-polythetic" approach towards disease diagnosis by adopting a dimensional approach (Cuthbert & Insel, 2013). Specifically, the RDoC framework offers a valuable lens for conceptualizing both the disorders and their risk factors by focusing on the underlying dysfunctions across psychological and biological systems (Böttger et al., 2023; Cuthbert & Insel, 2013). Within the RDoC, the Positive Valence System (PVS) is particularly relevant to anhedonia, as it encompasses systems involved in anticipating, acquiring, processing, and responding to pleasant or rewarding stimuli (National Institute of Mental Health, 2020; Olino,

2016). Reward anticipation prepares an individual for future positive events, whereas reward elaboration involves engaging with and processing the immediate reward, which is necessary for generating an appropriate response (Der-Avakian et al., 2015). Although these stages of reward processing are interconnected, they can be distinguished at both behavioral and neural levels (McFarland & Klein, 2009; Wang et al., 2022). Neuroimaging studies provide compelling evidence for this dissociation; however, the slow temporal resolution of fMRI may merge the adjacent neural activity, making it challenging to isolate specific stages of reward processing and thus highlighting the need for alternative techniques (Wang et al., 2020).

A frequently used approach is the event-related potentials (ERPs) which, due to their exceptional temporal resolution, can disentangle the temporally proximate yet psychologically distinct phases of appetitive processing (Glazer et al., 2018; Luck, 2014). Within this framework a commonly used task for investigating anticipation and elaboration of emotional stimuli is the S1-S2 task, in which a warning stimulus (S1) is separated by a fixed interval (ISI) from the following target stimulus (S2; Poli et al., 2007; Walter et al., 1964). In this task, three ERPs can be identified: Cue-P300, Stimulus Preceding Negativity (SPN), and Late Positive Potential (LPP), which are linked to affective engagement, anticipation, and elaboration, respectively (Brunia, 1988; Lang & Bradley, 2010; Novak & Foti, 2015). Research on affective modulation of those ERPs highlights their sensitivity to variations in stimulus valence and arousal, with consistently observed larger amplitudes for emotional trails compared to neutral ones, thereby underscoring their relevance in studying emotional processing (Brunia et al., 2011; Hajcak & Foti, 2020; Novak & Foti, 2015). In the context of depression, research has consistently shown blunted processing (i.e. anticipation and elaboration) of pleasant stimuli in both individuals diagnosed with depression

(McFarland & Klein, 2009; Olino, 2016; Wu et al., 2017) and those at risk for the disorder (Kujawa et al., 2014; Luking et al., 2016; McCabe et al., 2012).

Building on this, recent efforts aimed to explore whether depression and its vulnerability are specifically tied to alterations at distinct stages of appetitive stimulus processing. The most compelling evidence highlights deficits in appetitive stimuli elaboration, as indicated by lower LPP amplitude in response to pleasant stimuli among both individuals diagnosed with depression (Dell'Acqua et al., 2022; Proudfit et al., 2015) and those at heightened risk (Kujawa et al., 2012; Moretta & Messerotti Benvenuti, 2023) compared to controls. Studies employing the S1-S2 tasks and exploring engagement with appetitive stimuli reveal a similar trend, with diminished Cue-P300 amplitudes to rewarding stimuli observed in both individuals with clinical depression (Thompson et al., 2023; White et al., 2021) and those with anhedonia (Chen et al., 2018). In contrast, studies examining affective anticipation indexed by the SPN, offer a more complex picture: some report attenuated SPN responses to rewards (Ren et al., 2022, 2024), others note potentiation (Umemoto & Holroyd, 2017), while others find no significant differences in SPN amplitudes to rewards among individuals with depressive symptoms compared to controls (Thompson et al., 2023). Finally, while existing literature suggests a connection between appetitive processing and anhedonia, the specific alterations at distinct stages of emotional processing in anhedonia remain largely unexplored.

In view of this evidence, the current study aimed to explore appetitive picture processing in individuals with varying levels of anhedonia through the analysis of ERPs during an emotional S1-S2 task, thereby addressing the observed gap in the literature. Particularly, this work investigated the following hypotheses:

1. Higher levels of anhedonia were expected to be associated with reduced appetitive elaboration, as reflected in a blunted LPP amplitude in response to pleasant stimuli.
2. Higher levels of anhedonia were expected to be associated with reduced appetitive cue engagement and anticipation, as reflected in a blunted Cue-P300 and SPN amplitudes in response to pleasant stimuli.

Despite appetitive processing being the primary concern of this work, an exploratory analysis on the affective processing of unpleasant stimuli in anhedonia was also conducted. Finally, this study also examined whether the appetitive processing deficits were associated solely with anhedonia symptoms or generalize to non-anhedonia depressive symptoms.

## 3.2 Materials and methods

### 3.2.1 Participants

A cohort of 45 (31 females, mean (M) age = 21.7, standard deviation (SD) = 1.84, range = 19 – 26) Caucasian students at the University of Padova, Italy, voluntarily took part in the study. The recruited sample of participants was medically healthy and free from psychotropic medication, as determined through an ad-hoc anamnestic interview. Any current or past diagnoses of cardiovascular, neurological, or mental disorders were included as exclusion criteria. All participants had normal or corrected-to-normal vision and provided written informed consent before taking part in the study. The study adhered to the ethical principles outlined in the World Medical Association Declaration of Helsinki for research involving human subjects and received approval from the Ethical Committee of Psychological Research, Area 17, University of Padova (protocol no. 564-b). Participants were compensated with 25 euros for their time.

### 3.2.2 Psychological measures and experimental task

*Psychological measures*

To assess anhedonia symptoms the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) was employed. The SHAPS evaluates pleasure experience across four domains: interest/pastimes, social interaction, sensory experience, and food/drink. The scale comprises 14 items, such as "I would be able to enjoy my favorite meal" and "I would find pleasure in my hobbies and pastimes". Responses are rated on a 4-point Likert scale (from "Strongly agree" to "Strongly disagree"), with disagreeing responses scored as 1 point and agreeing responses as 0 points, yielding a total score ranging from 0 to 14. A cumulative score of 3 or above indicates diminished hedonic capacity, reflecting the presence of anhedonia symptoms.

To measure depressive symptoms the Italian version of the Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Sica & Ghisi, 2007) was utilized. The BDI-II is well-validated self-report questionnaire designed to assess the severity of depressive symptoms over the past two weeks. It is composed of 21 items, each scored on a 4-point Likert scale, yielding a total score ranging from 0 to 63, with higher scores indicating greater symptom severity. As per the Italian validation of the BDI-II, a score of 12 or higher was used to distinguish individuals with depressive symptoms from those without (Sica & Ghisi, 2007). To reduce the overlap between depressive and anhedonia symptoms, only BDI-II items unrelated to anhedonia (all except 4, 12, and 22) were summed (Joiner et al., 2003).

*Experimental task*

The experimental task consisted of an affective S1-S2 task during an electroencephalographic (EEG) recording. The entire paradigm was composed of 84 trials within

a single block following a structured sequence. Each trial commenced with a 500 ms baseline period featuring a white fixation cross, followed by a 1500 ms warning stimulus (S1) that signaled the imminent presentation of a target stimulus (S2) lasting 6000 ms. The warning cue (S1) indicated the emotional valence of the upcoming stimulus using distinct symbols: a plus for pleasant, a circle for neutral, and a minus for unpleasant. The cue and target were separated by a 4500 ms inter-stimulus interval (ISI). A variable inter-trial interval (ITI), ranging between 6000 and 8000 ms, included a white fixation cross identical to the baseline. Participants were instructed to attend to both the cue (S1) and the target stimulus (S2), with no motor response required for S2 (Figure 3.1). They were also informed that the emotional image would always be preceded by a congruent cue, which would anticipate its emotional valence.

The stimuli for this study consisted of 42 emotional images (600 × 800 pixels) sourced from the International Affective Picture System (IAPS; Lang et al., 1997), with an equal distribution across the three affective categories: pleasant (e.g., romantic couples, extreme sports), neutral (e.g., household objects, everyday scenes), and unpleasant (e.g., violent confrontations, predatory animals). To prevent presentation of images with the same emotional valence in consecutive trials, all stimuli were displayed in a semi-randomized sequence. The normative arousal ratings of pleasant and unpleasant images were matched (pleasant: M ± SD = 6.5 ± 0.3; unpleasant: M ± SD = 6.2 ± 0.6; $p = .11$), while both remained significantly more arousing than the neutral stimuli (neutral: M ± SD = 3.1 ± 0.5, all $ps < .001$). Towards the end of the experiment, participants were asked to rate the arousal and valence of all 42 images using a computerized version of the 9-Point Self-Assessment Manikin (SAM; Bradley & Lang, 1994).

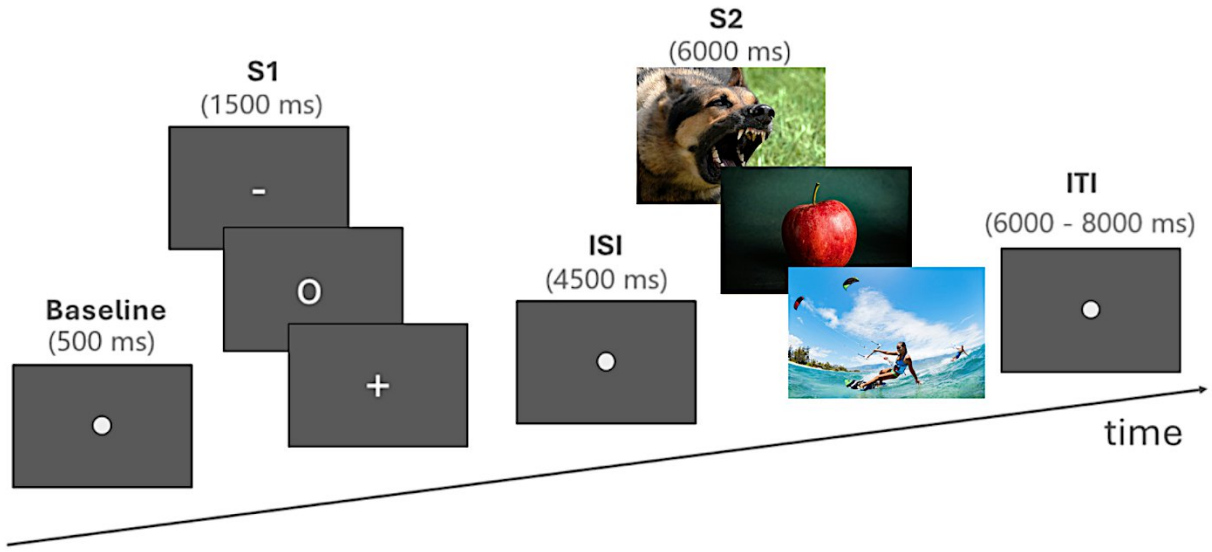


**Figure 3.1** Illustration of the S1-S2 task utilized in the study. ISI = inter-stimulus interval; ITI = inter-trial interval.

### 3.2.3 Procedure

The information about the study was distributed across the University of Padua campuses through fliers and online forums. Prospective participants were invited to complete an initial online screening questionnaire to assess their eligibility, which also included the SHAPS and BDI-II. Those meeting the inclusion criteria received an email to schedule their experimental session at the Department of General Psychology, University of Padua. To ensure optimal conditions for physiological measurement, participants were sent a text reminder the day before their session, specifying the scheduled time, date, and location, along with instructions to abstain from alcohol, caffeine, and drug consumption beforehand. Upon arrival, participants provided written informed consent and underwent a brief ad-hoc anamnestic interview. They were then seated in a dimly lit, sound-attenuated room in a comfortable chair. After electrode montage and a 3-minute resting state, they completed three practice trials, one for each emotional condition (pleasant, neutral, and

unpleasant), to familiarize themselves with the task. The experimental session then proceeded with the S1-S2 paradigm, with the entire laboratory procedure lasting approximately 90 minutes.

### 3.2.4 EEG recording and data reduction

Continuous EEG recordings were obtained using an ANT Neuro system and digitized with eego™ software (ANT Neuro, Enschede, Netherlands). The EEG data were collected via a 32-channel elastic cap fitted with standard Ag/AgCl electrodes (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, M1, and M2), based on the 10-20 system. During recording CPz served as an online reference. To monitor ocular artifacts, vertical and horizontal electrooculograms (EOGs) were recorded using a bipolar montage, with electrodes placed above and below the right eye and at the external canthi. Physiological signals were acquired in DC with a low-pass filter set at 30 Hz and sampled at 1000 Hz. The impedance levels at all electrodes were kept below 10 kΩ.

Offline preprocessing was conducted using MATLAB toolboxes EEGLab and Brainstorm (Tadel et al., 2011). To optimize computational efficiency, EEG data was first downsampled to 500 Hz and then re-referenced to linked mastoids. A bandpass filter of 0.01 to 30 Hz was then applied, followed by blink artifact correction using Independent Component Analysis (ICA). The continuous EEG signal was segmented into epochs spanning from 500 ms before S1 onset to 2000 ms after S2 offset, yielding 8500 ms epochs. Baseline correction was applied from -250 to -50 ms relative to S1. Artifact rejection was performed through a semi-automated procedure, which first excluded segments exceeding a 200 μV voltage threshold, followed by manual visual inspection to remove residual artifacts. In line with prior literature (Dell'Acqua et al., 2022; Novak et al., 2016; Poli et al., 2007; Schupp et al., 2003), visual inspection confirmed that the Cue-P300 and

LPP components were most pronounced over parietal sites, while the SPN exhibited maximal activity at frontocentral locations. Based on this, Cue-P300 was quantified as the peak amplitude across parietal electrodes (P3, Pz, P4) within a 200–400 ms time window post-S1 (Figure 3.3). The LPP was assessed as average mean amplitude over the same parietal electrode pool within a 500–1000 ms timeframe following S2 onset (Figure 3.3). Lastly, the SPN was measured as average mean amplitude at frontocentral sites (FC1, FC2, FC5, FC6) during the 200 ms preceding S2 presentation (Figure 3.4).

### 3.2.5 Statistical analyses

Statistical analyses were carried out in R Studio (R Core Team, 2023), using linear mixed-effects models implemented with the lme4 (Bates et al., 2015) and lmerTest (Kuznetsova et al., 2017) packages. A significance threshold of $p < .05$ was set for all analyses. All models included participants as a random intercept, and sex (biological) as a covariate to account for the sex unbalance within the experimental sample.

To examine the impact of emotional category and anhedonia on self-reported ratings of valence and arousal, two separate models were built. Each model included Category (pleasant, neutral, unpleasant), SHAPS scores, and their interaction as fixed factors: Model ← lmer(subjective ratings of arousal or valence ~ Category × SHAPS + Sex + (1|Subject)).

Then, to ensure the effect of emotional valence on the Cue-P300, SPN, and LPP, three separate models with Category as a fixed factor were conducted on each ERP: Model ← lmer(ERP amplitude ~ Category + Sex + (1|Subject)).

To test the primary hypothesis—namely the relationship between anhedonia levels and distinct stages of emotional processing—three separate models were conducted, one for each ERP

component (Cue-P300, SPN, LPP). Differential ERP scores (ΔERP; pleasant - neutral, unpleasant - neutral) were employed to reduce the number of predictors and isolate the effect of the emotional category. Each model included Category (pleasant, unpleasant), SHAPS scores, and their interaction as fixed factors: Model ← lmer(△ERP amplitude ~ Category × SHAPS + Sex + (1|Subject)).

In order to determine if these effects were uniquely tied to anhedonia symptoms, a comparable model was conducted with non-anhedonic depressive symptoms as the predictor. This model included Category (pleasant, unpleasant), BDI-II non-anhedonic scores, and their interaction as fixed factors, with sex as a covariate and participants as a random intercept: Model ← lmer(△ERP amplitude ~ Category × BDI-II non-anhedonic + Sex + (1|Subject)).

The fixed effects were assessed by reporting the estimated coefficients (b), standard errors (SE), t-values, and the corresponding confidence intervals. All predictors in the model were centered and scaled, and the p-values were calculated using the Satterthwaite approximation, as implemented in the lmerTest package. The collinearity among the predictors was evaluated by calculating the Variance Inflation Factors (VIF) using the vif function from the car package (Fox et al., 2019). Subsequently, significant main effects were analyzed through a Tukey HSD post-hoc tests to adjust for multiple comparisons.

### 3.3 Results

*Psychological measures and Valence and Arousal SAM ratings*

The SHAPS scores had an average of 1.8 (SD = 1.7, range = 0–6). For the BDI-II, the mean score was 13.82 (SD = 10.11, range = 1–45), while the non-anhedonia BDI-II score averaged 12.22

(SD = 8.86, range = 1–39). The mean and standard deviations of self-reported valence and arousal ratings (SAM) for pictures in each emotional Category are summarized in Table 3.1.

Linear mixed-effects models on self-reported SAM ratings revealed a significant main effect of Category in predicting valence ($F_{(2,1843)} = 907.15$, $p < .001$) (Figure 3.2). Specifically, subjective ratings of valence were significantly higher for pleasant images compared to neutral and unpleasant images (all $ps_{Tukey} < .001$), and significantly lower for unpleasant images compared to neutral images ($p_{Tukey} < .001$ ). However, neither SHAPS scores nor the interaction between Category and SHAPS significantly predicted valence ratings.

Linear mixed-effects models on self-reported SAM ratings revealed a significant main effect of Category in predicting arousal ($F_{(2,1843)} = 517.12$, $p < .001$) (Figure 3.2). Particularly, self-reported arousal ratings were significantly higher for both pleasant and unpleasant images compared to neutral ones (all $ps_{Tukey} < .0001$), but also for unpleasant compared to pleasant images ($p = .002$). Consistent with the valence model, neither SHAPS scores nor the interaction between Category and SHAPS had a significant effect on arousal.

**Table 3.1** Mean and standard deviation of valence and arousal SAM rating for pleasant, neutral, and unpleasant pictures.

| | | **Category** | | |
|---|---|---|---|---|
| | | **Pleasant** | **Neutral** | **Unpleasant** |
| **SAM ratings** | **Valence** | 6.78 ± 1.18 | 5.20 ± 1.30 | 3.17 ± 1.65 |
| | **Arousal** | 4.94 ± 2.37 | 2.47 ± 2.36 | 5.26 ± 1.68 |

Note. Data are M (SD).

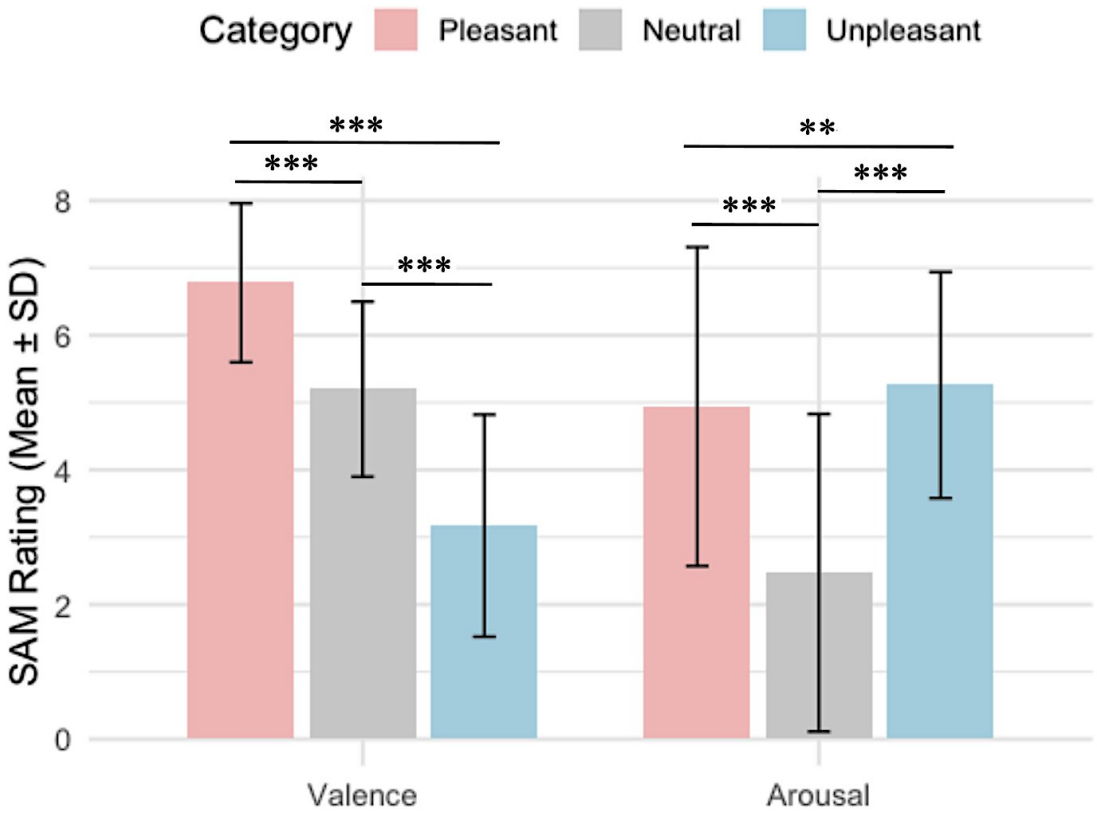


**Figure 3.2** Valence and arousal SAM rating for pleasant, neutral, and unpleasant pictures. Standard deviations are marked by error bars and asterisks indicate the level of statistical significance (*$p < .05$, **$p < .01$, *** $p < .001$).

*Emotional Condition and ERP amplitudes*

The linear mixed-effects models revealed significant effects of emotional Category on all the examined ERP components (Cue-P300, $F_{(2,358)} = 10.27$, $p < .01$; SPN, $F_{(2,487)} = 3.18$, $p = .04$; LPP, $F_{(2,358)} = 21.17$, $p < .01$). The mean ERPs amplitude in each emotional Category are reported in Table 3.2. The Cue-P300 peak amplitudes were significantly higher for pleasant images compared to both neutral ($p_{Tukey} < .0001$) and unpleasant conditions ($p_{Tukey} = .01$), while the difference between unpleasant and neutral images was not significant ($p_{Tukey} = .21$) (Figure 3.3). For the SPN, mean amplitudes were more negative for pleasant images relative to neutral ones ($p_{Tukey} = .03$), but no significant differences emerged between unpleasant and neutral conditions ($p_{Tukey} = .64$) or between pleasant and unpleasant images ($p_{Tukey} = .24$) (Figure 3.4). Lastly, LPP

amplitudes were significantly greater for emotional images, both pleasant and unpleasant, compared to neutral stimuli (both $ps_{Tukey} < .0001$). However, no significant difference was found in the LPP mean amplitude between pleasant and unpleasant images ($p_{Tukey} = .18$) (Figure 3.3)

**Table 3.2** Mean and standard deviation of the ERPs amplitude (μV) in each emotional Category (pleasant, neutral, and unpleasant).

| | | **Category** | | |
|---|---|---|---|---|
| | | **Pleasant** | **Neutral** | **Unpleasant** |
| **ERPs amplitude (μV)** | **Cue-P300** | 9.74 ± 4.06 | 8.59 ± 3.50 | 9.02 ± 3.84 |
| | **SPN** | 1.79 ± 5.15 | 3.08 ± 6.62 | 2.62 ± 5.95 |
| | **LPP** | 9.92 ± 7.09 | 7.30 ± 6.79 | 10.94 ± 8.97 |

Note. Data are M (SD).

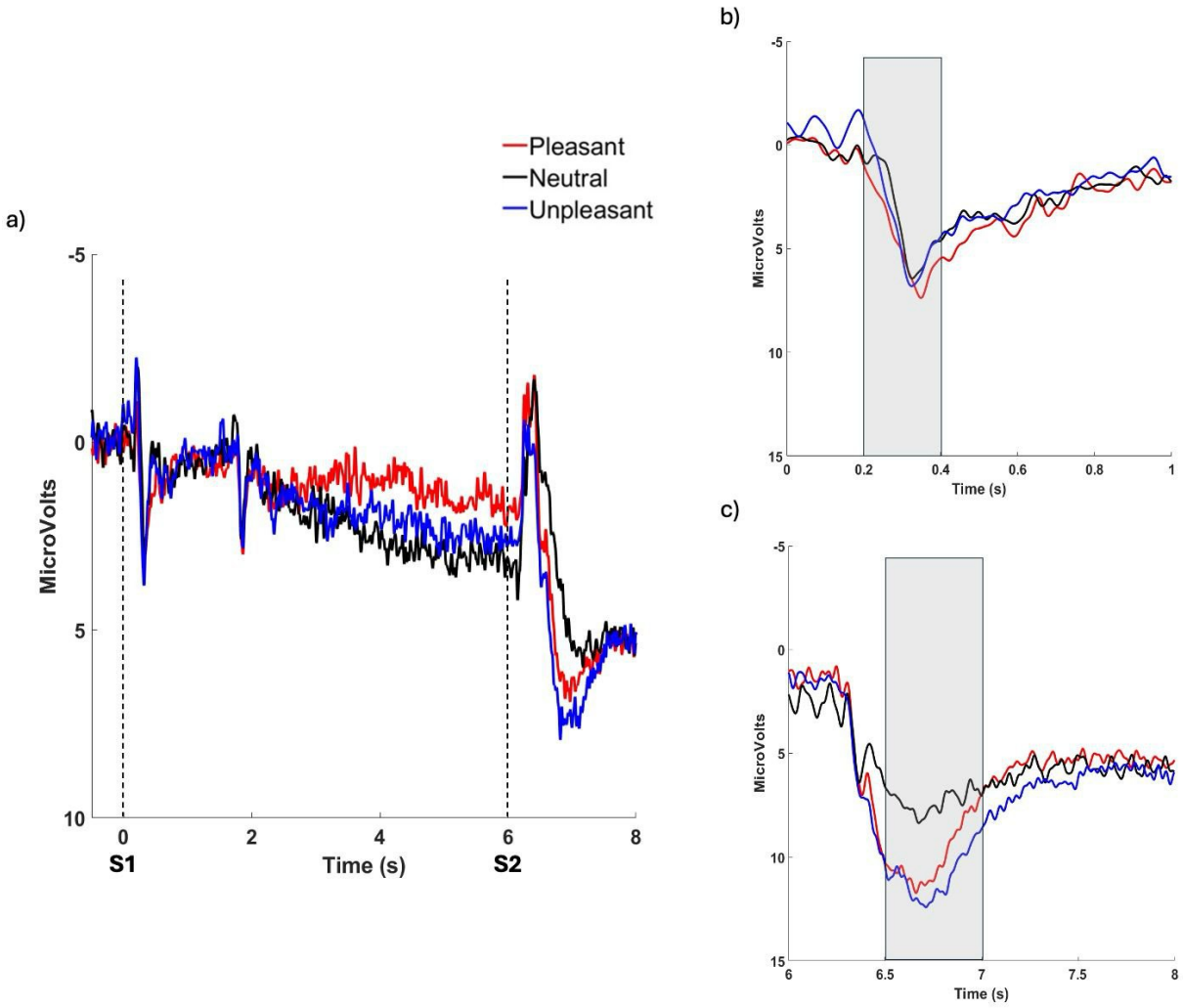


**Figure 3.3 a)** Grand-averaged ERP waveforms for an entire epoch trial, recorded at parietal sites (P3, Pz, P4) across all participants. The cue stimulus (S1) appeared at 0 s, followed by the target stimulus (S2) at 6 s. **b)** Grand-averaged Cue-P300 peak amplitude scored within the 0.2-0.4 s window. **c)** Grand-averaged LPP mean amplitude scored within the 6.5 – 7 s window.

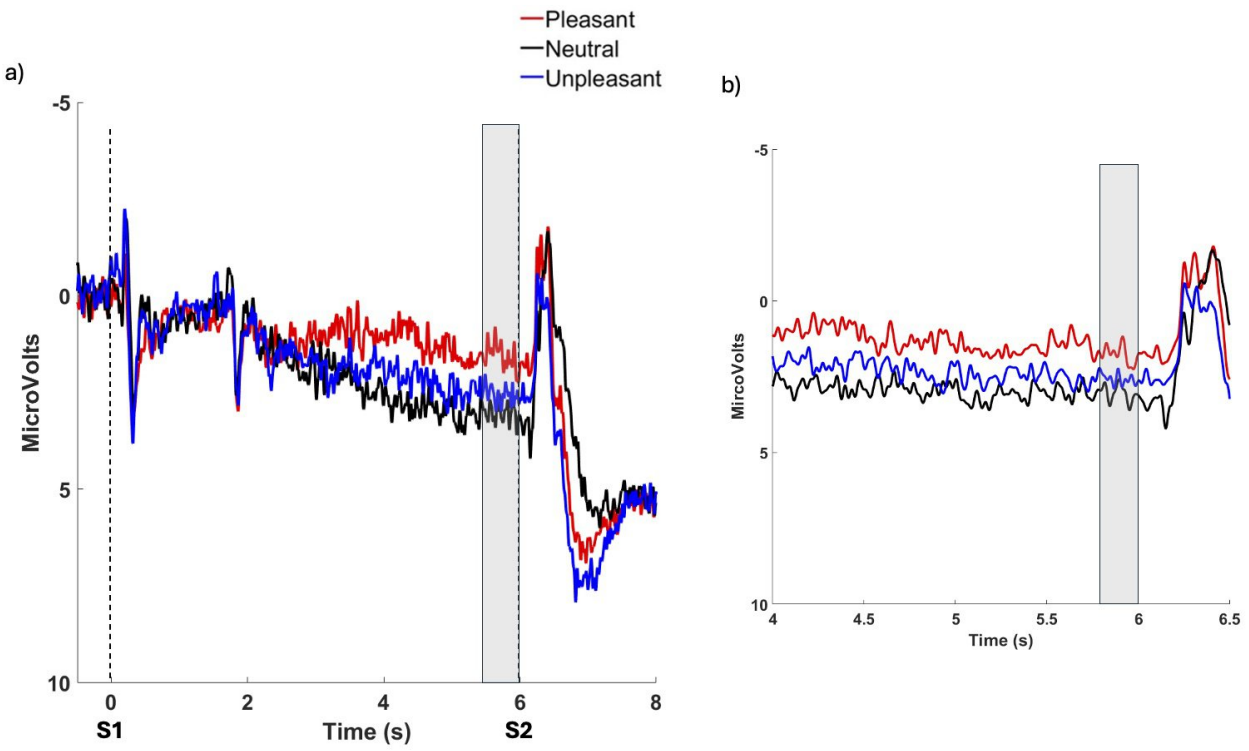


**Figure 3.4 a)** Grand-averaged ERP waveforms for an entire epoch trial, recorded at frontocentral (FC1, FC2, FC5, FC6) across all participants. The cue stimulus (S1) appeared at 0 s, followed by the target stimulus (S2) at 6 s. **b)** Grand-averaged SPN mean amplitude scored within the 5.8 and 6 s time window before S2.

*Anhedonia and the distinct phases of emotional processing*

The outcomes of the three mixed-effects models, which predicted ERPs amplitude from Category, SHAPS scores, and their interaction, are presented in Table 3.3. The collinearity analysis revealed that the predictors exhibited an acceptable level of multicollinearity, with VIF values all remaining below 1.22.

In the Cue-P300 model, neither SHAPS scores nor the Category × SHAPS interaction reached significance; only the main effect of Category was significant, with pleasant images eliciting a greater mean amplitude than unpleasant ones. In contrast, the SPN model revealed a significant Category ×SHAPS interaction effect, suggesting that higher anhedonia levels were associated with a more pronounced (i.e., more negative) SPN response to pleasant stimuli compared to

unpleasant ones (see Figure 3.5). Likewise, the LPP model showed a significant Category by SHAPS interaction, but in the opposite direction: greater anhedonia was linked to attenuated LPP amplitudes in response to pleasant images compared to unpleasant ones (see Figure 3.6).

The outcomes of the mixed-effect models predicting ERPs amplitude from Category, non-anhedonic BDI-II scores and their interaction are included in the Appendix (Table A1). Neither the effect of non-anhedonic BDI-II scores nor the Category × non-anhedonic BDI-II scores interaction showed significance.

**Table 3.3** Linear mixed-models predicting ERP amplitudes from emotional Category (pleasant, unpleasant), SHAPS scores, and their interaction. Category-unpleasant serves as a reference level. Significant effects are shown in bold and the asterisks indicate the level of statistical significance (*$p < .05$, **$p < .01$, *** $p < .001$).

| | b (SE) | t | *p* |
|---|---|---|---|
| *Cue-P300 model* | | | |
| **Category** | **0.72 (0.25)** | **2.87** | **< .01*****|
| SHAPS | .60 (0.39) | 1.51 | .13 |
| Category × SHAPS | 0.70 (0.81) | 0.86 | .39 |
| *SPN model* | | | |
| Category | -0.84 (0.57) | -1.47 | .14 |
| SHAPS | 0.13 (0.91) | 0.14 | .89 |
| **Category × SHAPS** | **-1.62 (0.58)** | **-2.80** | **< .01***** |
| *LPP model* | | | |
| Category | -1.02 (0.64) | -1.60 | .11 |
| SHAPS | 0.56 (0.81) | 0.69 | .49 |
| **Category × SHAPS** | **-1.99 (0.64)** | **-3.11** | **< .01***** |

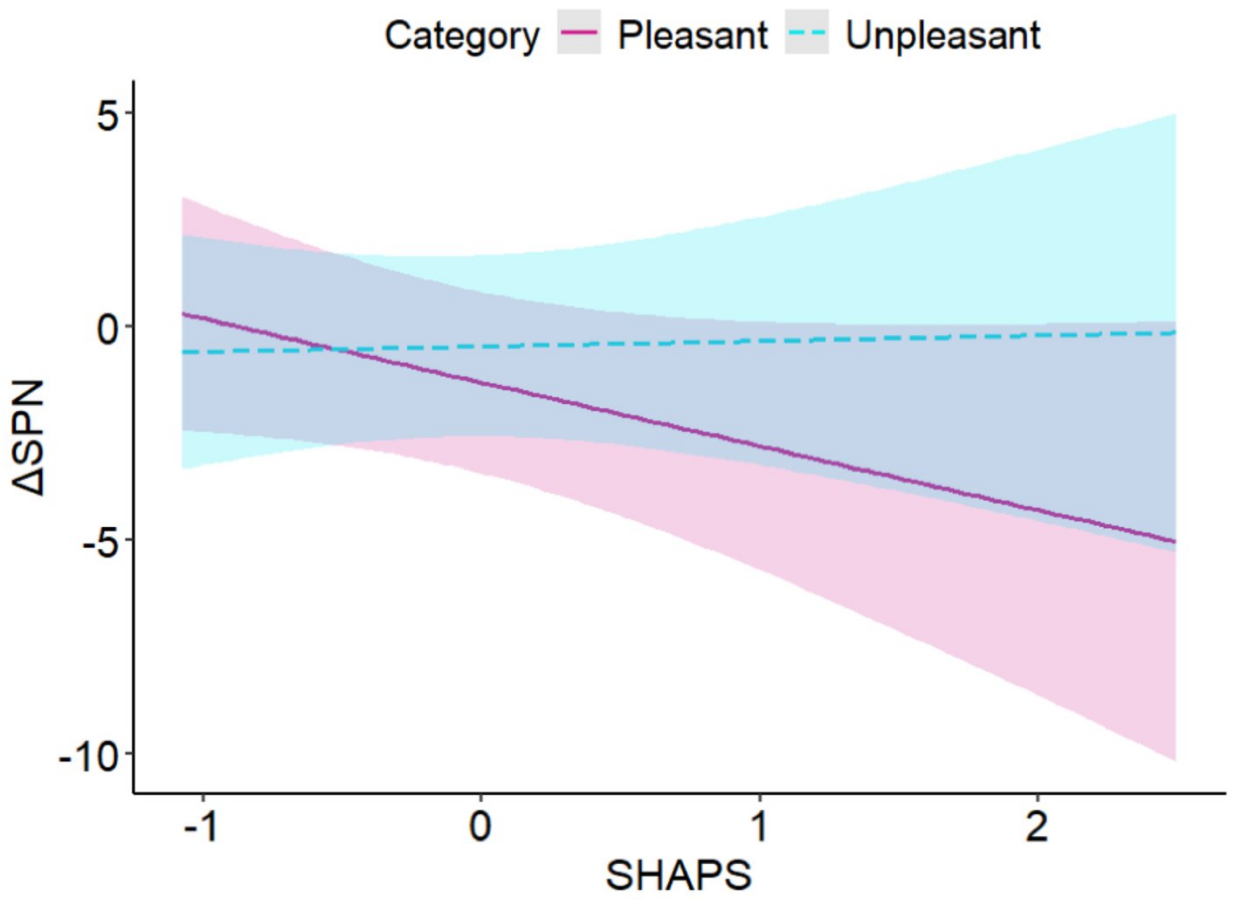


**Figure 3.5** Interaction effect of SHAPS (mean-centered values) and emotional category (pleasant, unpleasant) on ΔSPN amplitude. Ninety-five % confidence bands are presented in different colors.

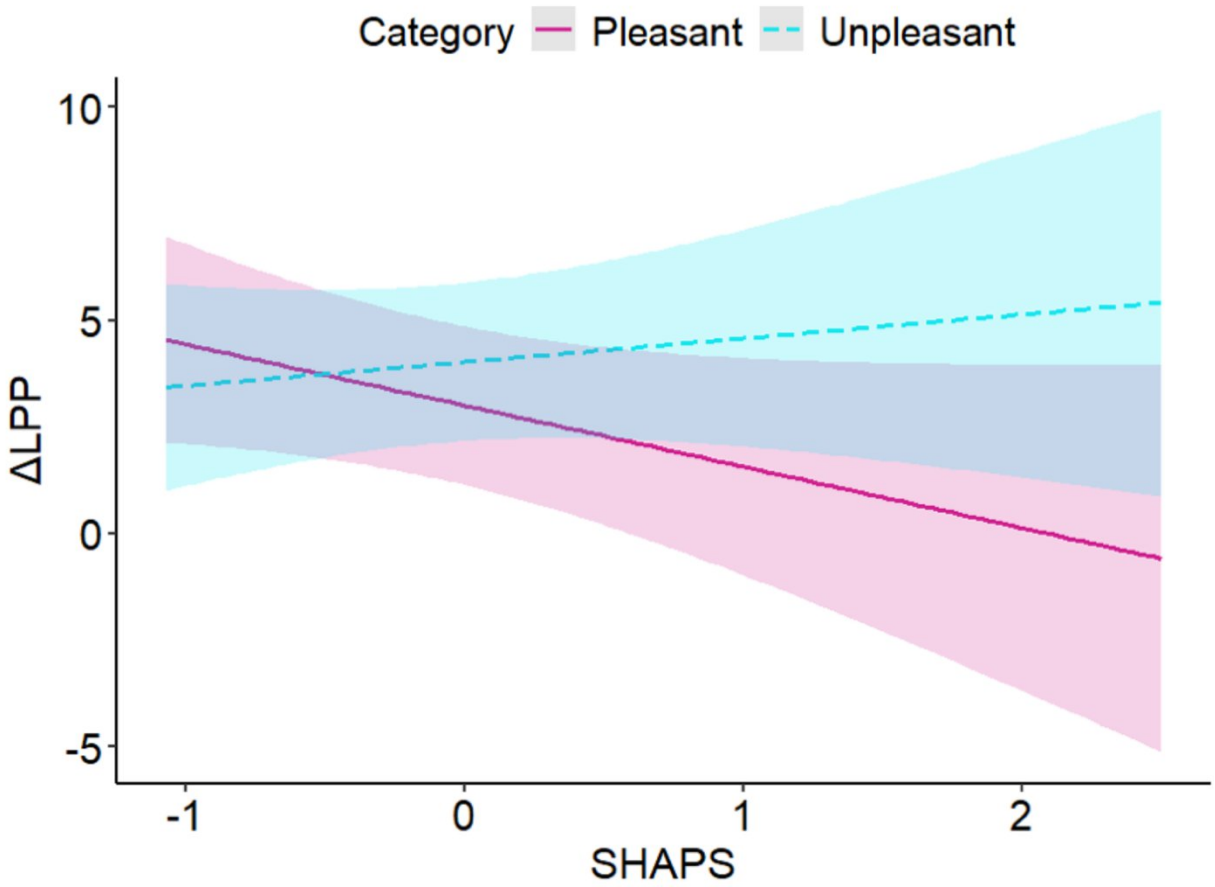


**Figure 3.6** Interaction effect of SHAPS (mean-centered values) and emotional category (pleasant, unpleasant) on ΔLPP scores. Ninety-five % confidence bands are presented in different colors.

### 3.4 Discussion and conclusions

This study aimed to investigate the multiple stages of appetitive processing in anhedonia using ERPs recorded during the S1-S2 task. The importance of exploring emotional processing in anhedonia stems from it being a significant risk factor for MDD onset and progression (Pizzagalli, 2014). Traditionally understood as a diminished ability to experience pleasure, anhedonia is now increasingly recognized as a broader disruption in reward processing, affecting not only pleasure itself but also the anticipation of rewards and the motivation to pursue them (Treadway & Zald, 2011). Building on this, this study sought to examine how anhedonia shapes distinct phases of affective processing: cue engagement, affective anticipation, and affective elaboration. Identifying

specific deficits could provide critical insights into the mechanisms underlying vulnerability to depression. Firstly, it was hypothesized that higher anhedonia levels would be associated with a reduced elaboration of pleasant stimuli, as reflected in a diminished LPP response. Furthermore, the second hypothesis expected blunted cue engagement and anticipatory responses to pleasant stimuli in higher anhedonia levels, indexed by attenuated Cue-P300 and SPN amplitudes respectively.

Consistent with the first hypothesis, individuals with higher levels of anhedonia exhibited dampened elaboration and reduced motivated attention toward pleasant stimuli. Specifically, participants with anhedonia showed lower LPP amplitudes in response to appetitive stimuli compared to healthy controls. These findings align with previous research demonstrating attenuated LPP responses to rewards and pleasant images in individuals with depression (Klawohn et al., 2021; Weinberg et al., 2016) and those at familial risk for the disorder (Moretta & Messerotti Benvenuti, 2023; Proudfit et al., 2015). Notably, reduced LPP amplitudes to positive stimuli have also been linked to depression in remission (Klawohn et al., 2021) and increased vulnerability to future depressive episodes (Levinson et al., 2019). Therefore, the present findings contribute to the literature on depression vulnerability, demonstrating that anhedonia involves deficits in appetitive elaboration similar to those observed in other at-risk populations and clinically depressed individuals, highlighting it as a significant risk factor. Notably, in this study, a reduced LPP to pleasant stimuli was specifically associated with anhedonia rather than non-anhedonic depressive symptoms, suggesting that this component may uniquely reflect anhedonia rather than general depressive symptomatology, at least in individuals without a formal diagnosis of depression.

Contrary to the second hypothesis, individuals with higher anhedonia exhibited heightened anticipation of pleasant stimuli, as evidenced by an enhanced SPN response. A possible explanation for the observed increased anticipation may be a compensatory attempt to counterbalance the reduced elaboration of pleasant stimuli. As evidenced by research on clinical samples, individuals with full-blown depression show a profound deficit encompassing both the anticipation and elaboration of appetitive stimuli (Epstein et al., 2006; Forbes et al., 2009). Indeed, individuals in depression remission (Dichter et al., 2012) as well as those with subclinical depressive symptoms (Umemoto & Holroyd, 2017) exhibit an analogous pattern of heightened anticipation of future rewards. The current work constitutes the only study showing this effect in an affective picture processing task, therefore additional research employing similar paradigms may be beneficial in elucidating appetitive anticipation in depression vulnerability such as anhedonia. Nevertheless, this finding should be interpreted with caution as the typical SPN negative waveform, consistently remained above the baseline level across all emotional categories, potentially due to the paradigm failing to trigger the appropriate anticipatory processes. Additionally, the insufficient engagement of anticipatory processes may stem from the maintained congruency between the cue (S1) and the valence of the subsequent emotional stimuli (S2), in line with previous literature (Buodo et al., 2012; Poli et al., 2007). Introducing contingency manipulations, in that violations, may lead to a deeper understanding of the anticipation and emotional processing dynamics.

The present study did not reveal a significant association between Cue-P300 modulation and anhedonia symptoms. This null finding challenges the second hypothesis, as no reduction in neural engagement with positive-predictive cues was observed among individuals reporting higher levels of anhedonia. Notably, this result appears to contrast prior studies reporting diminished

Cue-P300 amplitudes in anhedonic populations (Chen et al., 2018; Thompson et al., 2023). A key methodological difference, however, is that those studies incorporated a motor response to the subsequent stimulus, which may partly account for the discrepancy in findings. As a whole, the present findings suggest a pattern in anhedonic individuals characterized by heightened anticipation, reflected in larger SPN responses, followed by reduced elaboration of pleasant stimuli, indicated by smaller LPP amplitudes. These results build on the existing literature of diminished processing of positive stimuli in depression vulnerability (Kujawa et al., 2012; Moretta & Messerotti Benvenuti, 2023), yet the increased anticipatory response to appetitive cues offers a novel perspective on the peculiar dynamics of affective processing associated with anhedonia. Despite previous studies demonstrating reduced affective responding to both pleasant and unpleasant stimuli in individuals at risk for MDD (Kujawa et al., 2012; Kujawa & Burkhouse, 2017), suggesting a pattern of overall hypoactivation of both motivational systems (Bylsma, 2021), the current work proposes anhedonia symptoms to specifically impair the appetitive emotional processing.

The main effects of emotional category revealed significant differences across all ERPs. The LPP responses were larger for emotional pictures, both pleasant and unpleasant, as compared to neutral indicating increased elaboration of emotional content. Similarly, the Cue-P300 and SPN amplitudes were larger for pleasant pictures, but not unpleasant, compared to neutral, suggesting greater cue engagement and stimulus anticipation of pleasant stimuli. The present findings build on prior research reporting heightened Cue-P300 and SPN responses to rewards (Morís et al., 2013; Novak & Foti, 2015; White et al., 2021), demonstrating an overall pattern to engage with and anticipate appetitive stimuli, even when passively viewed.

The SAM ratings indicate that emotional images were rated as significantly more arousing than neutral ones, thereby validating the employed experimental paradigm. However, the self-report ratings of valence and arousal were not modulated by anhedonia levels. This finding suggests that ERPs may offer greater sensitivity by capturing attentional and emotional processes related to anhedonia, not revealed by self-report measures (Kujawa & Burkhouse, 2017; Moretta et al., 2021). Combining both subjective self-reports along with psychophysiological measures may be particularly beneficial in uncovering nuances in affective processing dynamics in depression vulnerability.

From a clinical standpoint, the present results offer a deeper understanding of anhedonia mechanisms crucial for the development of targeted screening and early intervention protocols. As evidenced in this work, anhedonia is associated with reduced elaboration of pleasant stimuli therefore approaches increasing reward exposure or behavioral activation techniques constitute a promising treatment avenue (Kanter et al., 2010). Indeed, some interventions emphasizing active pursuit of pleasant experiences (Craske et al., 2019), have been developed such as the Positive Affect Treatment (Craske et al., 2016), Amplification of Positivity (Taylor et al., 2020), and Behavioral Activation for Anhedonia (Nagy et al., 2020). All those approaches have a common goal to increase the PVS activation (Craske et al., 2019), thereby enhancing the elaboration of pleasant and rewarding stimuli in those with anhedonia (Alsayednasser et al., 2022; Craske et al., 2016, 2019; Nagy et al., 2020; Taylor et al., 2020). Incorporating psychophysiological methods such as ERPs may help evaluate how effectively these interventions influence affective processing. For instance, savoring, a regulation strategy aimed at enhancing and *extending* positive emotional experiences, has been shown to increase LPP responses to pleasant stimuli (Bryant, 1989).

Utilizing ERPs in future work may help improve assessments of vulnerability to depression and increase the precision of preventive as well as therapeutic strategies.

Several limitations should be acknowledged when considering this study. Firstly, the sample consisted exclusively of young university students, which constrains the generalizability of the findings to a broader population. While SHAPS is a well-validated measure (Franken et al., 2007), it primarily captures consummatory anhedonia and does not adequately assess other facets of pleasure experience deficits (Rizvi et al., 2016). Incorporating additional measures, such as the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006), which distinguishes between anticipatory and consummatory components of pleasure, may offer a more comprehensive understanding of how anhedonia relates to appetitive processing stages. Finally, the current study did not control for potential confounds such as anxiety symptoms, having had a depressive episode in the past, or parental history of depression, which are known to influence affective processing (Kujawa et al., 2014; Ubl et al., 2015; Weinberg et al., 2016). Accounting for these variables could help clarify whether the observed effects are specific to anhedonia.

In conclusion, this study showed that individuals with higher anhedonia levels exhibit a distinct pattern of initially heightened anticipation followed by reduced elaborative processing of pleasant stimuli. These findings extend the growing evidence that anhedonia shapes neural responses at various stages of appetitive processing. Clarifying the complex dynamic in affective processing linked to depression vulnerability may aid in informing targeted screening approaches and guide the development of personalized early interventions.

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## Appendix

**Table A1.** Linear mixed-models predicting ERPs amplitudes from emotional Category (pleasant, unpleasant), non-anhedonic BDI-II scores and their interaction. Category-unpleasant serves as a reference level. Significant effects are shown in bold and the asterisks indicate the level of statistical significance (*p < .05, **p < .01, ***p < .001).

| **Predictor** | **b (SE)** | **t** | **p** |
|---|---|---|---|
| Cue-P300 model | | | |
| Category | **0.72 (0.25)** | **2.87** | **<.01*** ** |
| **BDI-II non-anhedonic** | .50 (0.40) | 1.24 | .22 |
| **Category × BDI-II non-anhedonic** | -0.19 (0.25) | -0.75 | .45 |
| SPN model | | | |
| **Category** | -0.83 (0.58) | -1.42 | .15 |
| **BDI-II non-anhedonic** | 0.65 (0.91) | 0.70 | .48 |
| **Category × BDI-II non-anhedonic** | -0.28 (0.58) | -0.48 | .63 |
| LPP model | | | |
| **Category** | -1.02 (0.65) | -1.56 | 0.12 |
| **BDI-II non-anhedonic** | 0.80 (0.81) | 0.99 | 0.49 |
| **Category × BDI-II non-anhedonic** | -0.54 (0.65) | -0.83 | 0.41 |