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<th>Electrophysiological Signatures of Reward Processing in Anhedonia</th>
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<tr>
<td>Author</td>
<td>Family Name: Mallorquí, Particle: Aida, Division: Sant Pere Claver Health Foundation, Organization: Mental Health Services, Address: Barcelona, 08004, Spain, Division: Cognition and Brain Plasticity Group, ICREA and Department of Basic Psychology (Campus de Bellvitge) [Bellvitge Biomedical Research Institute], IDIBELL, Organization: L’Hospitalet de Llobregat, University of Barcelona, Address: Barcelona, 08097, Spain</td>
</tr>
<tr>
<td>Author</td>
<td>Family Name: Padrão, Particle: Gonçalo, Division: Sant Pere Claver Health Foundation, Organization: Mental Health Services, Address: Barcelona, 08004, Spain, Division: Cognition and Brain Plasticity Group, ICREA and Department of Basic Psychology (Campus de Bellvitge) [Bellvitge Biomedical Research Institute], IDIBELL, Organization: L’Hospitalet de Llobregat, University of Barcelona, Address: Barcelona, 08097, Spain</td>
</tr>
<tr>
<td>Corresponding Author</td>
<td>Family Name: Rodriguez-Fornells</td>
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### Abstract

Anhedonia is characterized by a reduced capacity to experience pleasure in response to rewarding stimuli and has been considered a possible candidate endophenotype in depression and schizophrenia. In this chapter we will focus on recent studies in which new electrophysiological brain measures (event-related brain potentials and oscillatory activity) have been used to understand the deficits in reward processing in anhedonic subclinical and clinical samples. The advantage of these neuroimaging techniques is that they provide time-sensitive measures that could be especially relevant to disentangle the differences between anticipatory and/or consummatory experiences of pleasure in anhedonia. Furthermore, because of the close interrelationship between reward and learning processes, we will review evidence showing how learning and reinforcement styles could influence the capacity to accurately anticipate positive rewarding experiences in anhedonics as well as in depressive patients. At the motivational level, this cognitive bias could be translated not only into an increased susceptibility to avoid potential negative events but also into a reduced tendency to seek positive experiences or rewards. This interpretation is therefore in agreement with the idea that the effects observed in anhedonia with regard reward processing are more related to anticipatory rather than consummatory processes.

### Keywords

Anhedonia - Depression - Reward processing - Feedback processing - Learning - Feedback-related negativity - Medial-frontal theta oscillatory activity - Beta–gamma oscillatory - Motivation
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or consummatory experiences of pleasure in anhedonia. Furthermore, because of the close interrelationship between reward and learning processes, we will review evidence showing how learning and reinforcement styles could influence the capacity to accurately anticipate positive rewarding experiences in anhedonics as well as in depressive patients. At the motivational level, this cognitive bias could be translated not only into an increased susceptibility to avoid potential negative events but also into a reduced tendency to seek positive experiences or rewards. This interpretation is therefore in agreement with the idea that the effects observed in anhedonia with regard reward processing are more related to anticipatory rather than consummatory processes.

**Keywords** Anhedonia • Depression • Reward processing • Feedback processing • Learning • Feedback-related negativity • Medial-frontal theta oscillatory activity • Beta–gamma oscillatory • Motivation

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
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<tr>
<td>BOLD</td>
<td>Blood-Oxygenation-Level Dependent contrast</td>
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<td>BRS</td>
<td>Brain Reward System</td>
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<td>DBS</td>
<td>Deep Brain Stimulation</td>
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<td>ERN</td>
<td>Error related negativity</td>
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<td>ERPs</td>
<td>Event-related brain potentials</td>
</tr>
<tr>
<td>FCPS</td>
<td>Fawcett-Clarke Pleasure Scale</td>
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<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>FRN</td>
<td>Feedback related negativity</td>
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<tr>
<td>MFN</td>
<td>Medial Frontal Negativity</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<tr>
<td>NAcc</td>
<td>Nucleus Accumbens</td>
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<td>OFC</td>
<td>Orbitofrontal cortex</td>
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<td>PAS</td>
<td>Chapman Physical Anhedonia Scale</td>
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<tr>
<td>SAS</td>
<td>Chapman Social Anhedonia Scale</td>
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<tr>
<td>SHAPS</td>
<td>Snaith–Hamilton Pleasure Scale</td>
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<tr>
<td>VMPFC</td>
<td>Ventro medial Prefrontal Cortex</td>
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**11.1 Introduction**

Anhedonia, described as the diminished motivation for and sensitivity to rewarding experiences, has long been considered a fundamental symptom of depression as well as a residual condition in schizophrenic patients. However many researchers and clinicians have observed its presence before the onset of the mentioned
disorders advocating for a possible implication of anhedonia in the development of both psychopathological conditions [1]. The current perspective on anhedonia and the latest advances in research are based on this view. From this perspective, anhedonia could be considered a vulnerability marker of depression and it is envisioned as a candidate psychopathological endophenotype that could help to understand the neurobiological and genetic bases of certain clinical phenotypes [2, 3].

Recent years have shown a renewed interest in the study of affective processes, particularly in the psychological and neural mechanisms that explain the interaction between goal-directed behavior, reward and motivation. One of the most important aspects that has been somehow neglected, and crucial to understanding motivated behavior, is individual differences in anhedonia. The concept of anhedonia refers to a reduction of the ability to experience pleasure [4, 5] as reflected in a diminished interest in rewarding stimuli and pleasurable events. Anhedonia has been described as a prominent symptom and potential trait marker of major depression [6] and is currently one of the two required symptoms for a diagnosis of major depressive disorder (MDD) [7, 8]. In addition, anhedonia is broadly studied in relation to schizophrenia and the negative symptoms spectrum [9, 10]. For example, in a recent report, nearly 37% of patients with MDD experience clinically significant anhedonia [11].

In this chapter, by adopting a personality-trait approach of anhedonia, we first review neuroimaging, behavioral and psychometric data supporting that anhedonia is related to impairment in the anticipation component of reward, leaving intact the consummatory and pleasure experience per se. We also review different neuroscientific studies showing to which degree learning and reward processing are implicated in the appearance of anhedonia. In this sense we will focus on recent evidence using electrophysiological measures (event-related brain components) associated to reward processing of the possible association between anticipatory reward processes and anhedonia.

11.2 The Trait of Anhedonia as an Endophenotype

The limited success of gene studies regarding mental health disorders has led to a more focused approach based on the identification of intermediate endophenotypes associated both with the genetic variance and the phenomenology of a given disorder [12]. In this sense, because of its clinical importance and substantial heridability [13], anhedonia has been considered an important candidate and putative endophenotype both for schizophrenic-like conditions and depression. Endophenotypes represent subclinical traits associated with vulnerability to expressing a determined mental disorder. They are heritable and state-independent, and can manifest in individuals whether or not illness is active [2, 14]. According to this, anhedonia cannot be considered exclusively as a state triggered by the onset of the pathology, nor a residual symptom developed by a progressive functional deterioration, but an endurable trait present before the appearance of the disorder and manifested also in both healthy and subclinical individuals.
Adopting this perspective, anhedonia as a trait has been characterized in clinical, sub-clinical and non-clinical populations, showing stable individual differences across time [1, 10]. Epidemiological studies consider clinical individuals as those affected by a given disorder or illness; on the other hand sub-clinical individuals are those affected with a mild form of a disorder that stays below the surface of clinical detection; finally non-clinical individuals are those who are healthy regarding a particular disorder. Several studies have addressed the issue of the persistence of anhedonia across time. The majority of them have evaluated clinical samples and their evolution over a given period of time. For example, a recent study followed a cohort of 49 MDD patients for 20 years and clearly showed relative stability of physical anhedonia over time in the six evaluations carried out [1]. These authors also identified that the severity of physical anhedonia was related to an increase in depressive symptoms, interpreting that trait anhedonia could be a useful behavioral marker for identifying at-risk cases of MDD. These results are partially in agreement with previous studies showing stability of physical anhedonia over time [15] even when improvements of depressive or psychotic symptoms were identified [10, 16, 17]. For example, in a cohort of 127 schizophrenic patients that were followed for 10 years, physical anhedonia was found to show intra-individual stability supporting the trait-like perspective [17, 18]. However, it is worth noting that the authors of this study found little relationship between physical anhedonia and positive, negative or depressive symptoms, supporting the idea that the anhedonia trait appears to be an independent construct. In a similar way, Horan and co-workers [10] also proposed that physical anhedonia shows the characteristics of a stable vulnerability indicator in recent-onset psychotic patients, being relatively stable across time (3 evaluations in 15 months) and showing only slight increases over time.

These authors reported also that changes in physical anhedonia did not covariate with clinical symptoms and remained persistently elevated even in a subsample of patients who achieved a fully remitted state (see for similar findings, [19, 20]).

To summarize, psychometric studies demonstrate a tendency to highlight the stability of the anhedonia trait and its presence before the onset of the depression or psychosis in a similar way as some neurocognitive or neurophysiological deficits that have been identified as candidate endophenotypes for vulnerability in schizophrenia [21]. Moreover its endurance over time has been related to a poorer functional status in schizophrenia pointing out its possible relation with those schizophrenic forms characterized by severity of negative symptoms and cognitive/behavioral disorganization (‘negative’ or ‘deficit’ syndromes; [11, 18]).

11.3 The Measurement of Hedonic Trait and State

Self-reported measures of trait anhedonia have been actively used in many research studies with the aim of underpinning “anhedonia” and “hedonic capacity” as a psychopathology vulnerability trait stable over time. Briefly, in 1976, Chapman and Chapman [22] published a pair of scales with the aim of measuring
anhedonia as a characteriological defect in the ability to experience pleasure as observed in the poor premorbid adjustment of some schizophrenic patients [22]. These authors distinguished between physical and social anhedonia, the former being associated with sensitive pleasures (e.g., eating, touching, sex, etc.…)(measured using the Physical Anhedonia Scale, PAS, 61 items, yes-no responses) and the later with interpersonal interactive situations (measured using the Social Anhedonia Scale, SAS, 45 items). These items were worded so that they cover long-standing characteristics of anhedonia throughout the lifetime (e.g., ‘the taste of food has always been important to me’ for physical anhedonia, and ‘Getting together with old friends has been one of my greatest pleasures’ for social anhedonia). The higher the score on both scales, PAS or SAS, means increased anhedonia in a particular subject. The reliable psychometric properties of both scales, especially the PAS, have been demonstrated in several studies, all of them reaching an internal consistency parameter over 0.80 [1, 10, 17]. Even though there is active and current usage in anhedonia studies of the PAS due to its trait-centered measurement and extensive content coverage, some limitations of the instrument are worth mentioning. The content of some items is outdated (e.g. “I have always found organ music dull and unexciting”) and there is some content overlap between both instruments (e.g., ‘sex items are included in both instruments’). Furthermore, some items are worded negatively, so its rating can induce confusion. Finally the length of the administration (especially for the PAS) makes its usage not completely optimal in clinical settings. Interestingly, the anhedonia trait measured using the PAS in non-clinical populations offers a normal distribution, as has been reported in many studies.

Fawcett et al. [15] developed another self-reported psychometric instrument for the measurement of the current hedonic state known as the Fawcett-Clark pleasure scale (FCPS; 36 items, 5-point rating scale). In this case, the authors were interested in anhedonia as a temporary state conditioned by the severity of depression. This scale evaluates different situations like winning the lottery, sexual climax, a tender hug from spouse, etc. The higher the score on the test, the more vigorous was the hedonic capacity of the person.

Another well-known self-rated instrument is the Snaith-Hamilton Pleasure Scale (SHAPS, 14 items; 4-point agreement) originally developed to assess the hedonic tone or enjoyment in engaging certain common situations experienced during the last week (e.g. “I would enjoy my favorite television or radio program”) in both clinical and non-clinical populations [23]. The instrument was designed to overcome some of the limitations of the PAS, for example its cultural bias and the length of its administration. The items selected cover four domains of hedonic experience: interests, social interaction, sensory experiences and food/drink pleasures. Higher scores indicate less hedonic tone, i.e. more anhedonic levels. A recent study demonstrated very good internal consistency of the SHAPS and the ability to discriminate between clinical and non-clinical individuals [24]. Albeit laudable, the author’s effort to build a non-culturally biased instrument seems a difficult point to be attained given that pleasure, from its very experience to its continuous acquisition via learning, is always shaped by culture.
The self-reported instruments mentioned so far were designed to measure online hedonic capacity, i.e. the capacity to experience pleasure *per se* or what has been identified as consummatory pleasure. But the motivational aspects that guide goal-directed behavior and pleasure anticipation have been somewhat neglected at a psychometrical level. The Temporal Experience of Pleasure Scale (TEPS; 18-items, 6-point rating) represents an advance in this regard [25, 26]. These authors aimed to distinguish between the consummatory (e.g. “I appreciate the beauty of a fresh snowfall”) and anticipatory components of pleasure (e.g. “When ordering something off the menu, I imagine how good will it taste”) focusing exclusively on sensory and physical experiences. Higher scores on the both TEPS subscales indicate persons with high hedonic tone. The TEPS distinguishes individuals with a diminished ability to experience anticipatory pleasure from those with a consummatory pleasure deficit. There was only a 10% of overlap in both subscales indicating the convenience of measuring distinctive aspects of the complex and multifaceted constructs of reward and hedonic capacity. Although its optimal length and advance in parsing reward phases, the final version of the TEPS seems to neglect some aspects central to pleasure and reward in humans (e.g. sex or eating your favorite meal are not included in the consummatory subscale). Furthermore it is unclear if the anticipatory factor of this scale is more centered in measuring the experience of pleasure when anticipating rewards than the construct of reward motivation, which is more related to its behavioral component (triggering reward-seeking behaviors).

Other anhedonia studies have used clinical depression scales to measure the construct of anhedonia. For example, some authors have used the Beck Depression Inventory, and more precisely the analysis of the four items related to pleasure experience and loss of interest [27, 28]. Other studies have used the item#17 of the Hamilton Depression Scale. Finally, another instrument used with similar aims is the Mood and Anxiety Symptom Questionnaire [29] that includes some items related to lowered positive affect and interest related to anhedonia aspects [30, 31]. The fact that these instruments were designed to measure depression severity in patients could clearly affect the measurement of this trait in healthy samples.

Finally an often cited confirmatory factor analysis conducted with some of the mentioned scales and some other symptom measures that aimed to measure hedonic capacity in depression, encountered three distinct latent variables: hedonic capacity, anxiety and depression [27]. These results demonstrated different loadings of the hedonic scales on the hedonic capacity factor, and for example, the SHAPS and the FCPS showed more communality with the factor of hedonic capacity than the PAS. One possible explanation provided by the authors relied on the fact that the PAS is a trait measure of enduring characteristics while the other scales are more centered in a short temporal domain (right now or in the last few days). Further research is clearly needed in this domain to improve the assessment of the complex concept of hedonic capacity.
11.4 Pleasure, Reward and Its Different Components: From Theoretical to Empirical Studies

Reward processing is not a unitary construct and can be divided into distinct psychological, neural, and neurochemical subcomponents to understand its functioning [32, 33]. At the psychological level, our desire to maximize rewards and to minimize negative possible outcomes is an important drive of human behavior and we are constantly trying to identify and seek possible cues in the environment which might predict the possible appearance of rewards or negative outcomes, as well as instrumental behaviors which could cause the appearance of these outcomes. The association of an event with a reward or a punishment therefore constitutes a powerful learning signal. In addition, we use information from the feedback signals elicited by our actions to influence our future decisions. However, in ambiguous situations in which different outcomes are probable or when feedback information is not available, humans might need to make decisions which can be considered risky, erratic or impulsive. Interestingly, the cognitive processes required for successful adaptation in these situations might require the elicitation of affective responses (emotional valuation), the ability to associate neutral events to the appearance of an emotionally-charged outcome (learning) and the ability to store this information in order to make predictions (memory). Importantly, this intersection between affective processes, learning and memory is a core aspect of reward processing, motivated behavior and decision making in humans [34].

At the neural level, the Brain Reward System (BRS) is an important extended neural network of cortical-subcortical structures and circuitries involved in the regulation of motivational states, anticipation and prediction of reward, the pleasure triggered by a sensory event and finally the modulation of this subjective experience via other complex cognitive processes [35]. Thus, an interaction from external and internal conditions is needed to fulfill what is currently known as reward processing. Some stimuli (i.e., primary reinforcers) have innate strong interactions with the BRS (e.g. food, liquids) while others (i.e., secondary reinforcers) are weakly related but have the potential to acquire their rewarding properties through a process of association and learning with a primary reinforcer (e.g. money, drugs) [34, 36]. The neural bases of the BRS have been well described by many studies during the last decade (see for review, [32, 34, 36–44]). The utilization of different neuroimaging techniques during reward processing have allowed the identification of increments of the hemodynamic signal in a common set of regions in the mesocorticolimbic circuits: The ventral striatum (including the nucleus accumbens, NAcc), the amygdala, prefrontal cortex (including the orbitofrontal cortex – OFC, ventromedial prefrontal cortex -VMPFC or the anterior cingulate cortex – ACC), as well as the hippocampal, hypothalamus and insular cortex [45, 46]. This network is not only implicated in reward consumption but in learning, memory and motivation processes (see Fig. 11.1 for a schematic differentiation between the reward-motivation circuit and the learning-memory subcomponents; from [48]).
Figure 11.2 shows an illustration of the brain regions usually activated in monetary gambling tasks in which the outcome (monetary gains or losses) were unpredicted (see Fig. 11.2a). Notice that a broad network of brain regions are activated and that an extensive overlap is shown for the processing of both monetary gains and losses (Fig. 11.2b) (see [51] for a recent meta-analysis of the BRS). Advanced functional connectivity analyses in this study showed an extensive network of regions supporting similar responses to reward and punishment valuation including the insular cortex and OFC, the amygdala, the hippocampus and the SN/VTA midbrain regions. Besides, the crucial comparison between gains vs. losses showed the activation in one of the core regions of reward processing, the ventral striatum (including the NAcc; see also the reconstruction of the BOLD (Blood-Oxygenation-Level Dependent contrast) response for gains and losses in this region, Fig. 11.2c, d; [49]). The ventral striatum is an important center for the regulation of reward-appetitive and consummatory behaviors and its activity is modulated by (i) the presence of unpredicted positive and negative reward outcomes (e.g., monetary gains and losses) [48], (ii) when an expected reward is not received (decreasing its activation) and depending on the amount of the potential loss [52], (iii) anticipation of reward,
learning and motivation manipulations [34, 37, 43], and (iv) individual differences in the preferences of delayed versus immediate rewards [53]. The NAcc has also been implicated in addictive and impulsive decision making [54]. Notice, that the NAcc is a key integrative region weighting the different inputs coming from cortical areas (OFC, vmPFC – ACC, dorsolateral prefrontal cortex, insula), limbic regions (amygdala, hippocampus; [55] and midbrain [substantia nigra (NS)/ventral tegmental area (VTA)] and therefore modulating the selection of appropriate responses and goal-directed behavior [39, 56, 57]. Moreover, the direct interactions of the medial prefrontal cortex (ACC) and the ventral striatum (both receiving dopamine input from the midbrain through the mesocortical and mesolimbic pathways, respectively) allow having interacting loops requested for the proper adjustment of behavioral patterns [58]. Indeed the VMPFC/ACC regions might have an important role integrating motivational and cognitive inputs into behavioral adjustments and decision making.

Fig. 11.2 (a) Sequence of stimulus and response events in the gambling task used in our laboratory for fMRI reward gambling studies [48–50]. After a warning signal, a pair or numbers ([5, 25] or [5, 25]) is presented and participants are forced to select one of the numbers by pressing the corresponding button with the left or right hand (response choice). One second after the choice, one of the numbers turn red and the other green (feedback) indicating, respectively, a loss (red) or gain (green) of the corresponding amount of money in Euro cents. (b) fMRI brain activations observed for monetary gains and monetary losses using the gambling paradigm (Adapted from Ref. [48]). Notice the large increase of activation observed in the ventral striatum (nucleus accumbens, NAcc), prefrontal cortex (including the orbitofrontal cortex – OFC, ventromedial prefrontal cortex – VMPFC or the anterior cingulate cortex – ACC) as well as insular cortex [48]. (c) Gain-versus-loss contrast superimposed on the group-averaged T1 MRI image in standard stereotactic space. On the right (d), representation of the BOLD time course reconstruction at the peak of the NAcc showing the differences in activation between gain and loss trials [49].
Currently one of the most influential approaches has been proposed by Berridge and collaborators [32, 35, 59]. These authors have introduced the distinction between “wanting” and “liking” components of reward based on a growing body of literature that shows different neural networks and neurotransmitters involved in consummatory and anticipatory phases of goal-directed motivation. The “liking” component is associated to the experience of pleasure, i.e. the hedonic impact of reward, while the “wanting” component is associated to the desire for pursue certain rewards and its anticipatory aspects (predictions about future rewards). For the “wanting” component, reward learning and reinforcement processes are crucial for remembering, updating and creating new associations and predictions (conscious goals) about future and potential rewards or desires based upon past experiences [32]. Dopamine has been proposed to be involved in both anticipatory and consummatory processes, although the current view favors the crucial role of this neurotransmitter in guiding reward prediction processes (“wanting” aspects) [59]. Indeed, recent research has shown that depletion of dopamine does not affect consummatory reactions, whereas the opioid and the gamma-aminobutyric acidergic systems in the ventral striatum are important in regulating the experiences of pleasure [60–63]. The “wanting” and “liking” components also belong to different temporal phases of motivated behavior [64]. The former is related with the appetitive, preparatory or anticipatory phases that are reflected in approach, instrumental or reward-seeking behaviors. In contrast, the “liking” component corresponds to a consummatory phase, that is, the actual interaction with the rewarding object (e.g., eating, drinking, etc.). Any impairment regarding any of the cited behaviors (e.g. a difficulty predicting the availability of an impending reward or an incapacity to integrate new sources of reward) could lead erroneously to the impression that a person is experiencing a simple loss of pleasure although the reward receipt/consumption could still be experienced as pleasurable [65].

Finally, it is important to mention that recent research has also highlighted the role of the amount of activation or invigoration of the organism in the anticipatory stages of motivated behavior in order to pursue particular desires or to engage in reward-seeking or goal-directed behaviors (see for a review, [43]). Indeed, this distinction between “activational” (vigor, persistence, maintancene of sustained activity) and “directional” (behaviors directed to a particular goal or stimulus) aspects of motivation is rather old in the field of psychology [66]. The activational aspects of motivated behavior are reflected in the amount of resources and substantial effort that can be invested in reward-seeking behaviors, especially considering that in some cases, there is a long temporal distance between the pursued goal and effort required to be sustained over long periods of time. Several studies have shown the importance of mesolimbic dopamine in the NAcc in the regulation of reward-related effort [43]. For example, it has been observed that in rats, dopamine depletion in the NAcc decreases the response for obtaining larger rewards that require more effort, but in contrast, it increased the amount of responses for smaller rewards that required less effort [67]. Similar results has been observed in humans, in which transient attenuation and potentiation of dopamine can decrease or increase the motivation to work for rewards [68, 69].
In summary, the most recent investigation of the behavioral and neural bases of reward-related behavior have provided a rich and multifaceted picture in which overlapped and distinct neural networks are involved in different subcomponents of reward processing as, for example, the hedonic impact of pleasurable experiences, affective valuation of rewards, reward anticipation, reward-seeking motivational aspects and the complex interaction between these processes in actual decision making.

11.5 Anhedonia in Brain Imaging Studies: Neural Substrates of Reward Parsing

Some studies have tried to link depression with a dysfunction relating the BRS, but only a few of them were focused exclusively on anhedonia. The majority of them present results obtained from depressed samples with high anhedonic symptoms. The tradition of studying anhedonia in the context of depressive disorders has been great in mental health and neuroscientific literature. In this section these studies will be briefly reviewed and presented chronologically (see Table 11.1 for a summary). In this manner, it is possible to show the evolution of the anhedonia-brain reward dysfunction hypothesis that runs from mere brain activation exploratory studies to new research oriented to connect specific brain regions and networks with more fine-grained subcomponents of reward (see previous section). It is worth mentioning that only three studies to our knowledge dealt with healthy populations in relation to the study of anhedonia and reward [30, 31, 72]. The existing literature of anhedonia in psychotic disorders and its relation to the BRS has increased significantly during recent years although the onset of this research approach has been slow compared to the study of MDD and reward (see [78–82]).

The first study to relate anhedonia with alterations in the BRS was conducted by Mitterschiffthaler and co-workers [70]. These authors wanted to explore whether anhedonia was related to a lack of activation in the brain regions related with pleasure or to abnormal overactivation in other regions. With this aim in mind, seven unipolar depressed female patients were compared to a control group while observing positive emotional stimuli inside the scanner. The results showed differential recruitment of frontal areas in the two groups when exposed to positive stimuli. Patients displayed significantly more activation in lateral OFC areas and the ACC than the control group. The authors argued that the frontal hyperactivation in high anhedonic patients might represent an attempt to experience positive emotions. Increased BOLD signal in the putamen was also encountered in the patient group, which was interpreted as a medication effect.

Two years later, Keedwell and cols. [71] explored anhedonia severity and its neural correlates in depressed individuals using an autobiographical memory task. Several structures related to reward processing were implicated in the processing of positive emotionally charged stimuli, as for example the VMPFC in higher anhedonic individuals. Those participants who felt happier as a reaction to positive
Table 11.1  Summary of the neuroimaging studies related to reward processing and anhedonia reviewed in the text

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample</th>
<th>Technique</th>
<th>Anhedonia measure</th>
<th>Task</th>
<th>Activated regions in anhedonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitterschiffthaler et al. [70]</td>
<td>2003</td>
<td>7 female depressed patients</td>
<td>fMRI</td>
<td>FCPS</td>
<td>IAPS Picture Attentive Observation</td>
<td>Increased activation in frontal lobes, thalamus, basal ganglia and insula</td>
</tr>
<tr>
<td>Keedwell et al. [71]</td>
<td>2005</td>
<td>12 MDD patients</td>
<td>fMRI</td>
<td>FCPS</td>
<td>Mood Provocation Paradigm (using autobiographical memories)</td>
<td>VMPFC and Anterior Caudate (in front of + stimuli)</td>
</tr>
<tr>
<td>Harvey et al. [72]</td>
<td>2007</td>
<td>29 non-clinical adults</td>
<td>fMRI/VBM</td>
<td>PAS</td>
<td>Emotional Memory Task as covert emotional processing using IAPS stimuli</td>
<td>VMPFC activation (for + stimuli) and volumetric reduction in the Anterior Caudate</td>
</tr>
<tr>
<td>Schlaepfer et al. [73]</td>
<td>2008</td>
<td>3 resistant MDD patients</td>
<td>PET</td>
<td>Subject Verbal Report</td>
<td>No task. Deep Brain Stimulation in NAcc (ventral striatum)</td>
<td>NAcc, Amygdala, DLPFC, DMPFC increased metabolism. Ventral and VLPFC decreased metabolism.</td>
</tr>
<tr>
<td>Heller et al. [74]</td>
<td>2009</td>
<td>27 MDD patients</td>
<td>fMRI</td>
<td>None</td>
<td>Emotion Regulation Paradigm by cognitive appraisal using IAPS stimuli</td>
<td>NAcc decreased activation across the task in front of positive stimuli. Reduced connectivity between NAcc and Left Middle Frontal Gyrus</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Imaging Techniques</td>
<td>Referring Measure</td>
<td>Task</td>
<td>Findings</td>
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<tr>
<td>Pizzagalli et al. [75]</td>
<td>2009</td>
<td>30 MDD patients</td>
<td>fMRI/VBM</td>
<td>BDI items referred to anhedonia</td>
<td>Monetary Incentive Delay Task</td>
<td>Left NAcc decreased activation when processing positive outcomes. Reduced Caudate volume bilaterally</td>
</tr>
<tr>
<td>Wacker et al. [31]</td>
<td>2009</td>
<td>33 non-clinical adults</td>
<td>Resting EEG/ fMRI/ Volumetry</td>
<td>MASQ-AD</td>
<td>Monetary Incentive Delay Task</td>
<td>NAcc decreased activation in front of + stimuli. NAcc volume reduction</td>
</tr>
<tr>
<td>Robinson et al. [76]</td>
<td>2012</td>
<td>13 MDD patients</td>
<td>fMRI</td>
<td>None</td>
<td>Reversal Learning Task</td>
<td>Right Putamen activation attenuated on unexpected rewards</td>
</tr>
<tr>
<td>Dowd et al. [77]</td>
<td>2012</td>
<td>29 patients with schizophrenia or schizoaffective disorders</td>
<td>fMRI</td>
<td>PAS and SAS</td>
<td>Pavlovian Reward Prediction Task</td>
<td></td>
</tr>
<tr>
<td>Keller et al. [30]</td>
<td>2013</td>
<td>21 non-clinical adults</td>
<td>fMRI/Effective connectivity</td>
<td>PAS, SAS and MASQ-AD</td>
<td>Listening to familiar and unfamiliar musical pieces</td>
<td>Reduced reactivity and connectivity of the mesolimbic reward system. Decreased activation in NAcc, basal forebrain, hypothalamus, OFC and anterior insula</td>
</tr>
</tbody>
</table>
stimuli showed larger activation in the striatum (bilateral anterior caudate). The authors interpreted these findings considering that the frontal hyperactivity was due to an attempt to get into a happy mood particularly in the case of anhedonic participants [71]. According to more recent findings and the implication of the VMPFC in cognitive control and conflict monitoring [83, 84], we can also consider that this hyperactivation in highly anhedonic participants could be due to an increase in cognitive control due to the fact of viewing positive information; that is, the expected mood in front of the positive stimuli is not reached by the participant.

Harvey et al. [72] addressed the study of anhedonia as a trait in a non-clinical sample. Parallel to the previous study, participants underwent an emotional memory task [using the emotional pictures from the IAPS (International Affective Picture System)]. In agreement with previous studies, hyperactivation of the VMPFC in front of positive stimuli was found to be positively correlated with the anhedonia trait that was interpreted in the same vein as in the previous study. What’s more, a volumetric reduction in the anterior caudate was also found, advocating for impairment in both motivational and hedonic systems [72]. The authors interpreted these results in relation to a possible dysfunction of the pleasure experience as well as a decreased willingness to engage in pleasurable activities. Thus, no differences between anticipation and consummation phases of reward processing were considered.

Schlaepfer et al. [73] reported that Deep Brain Stimulation into the reward circuitry ameliorated anhedonia symptoms in three patients affected with treatment resistant major depression. The patients received stimulation at increasing voltages for 7 days and were scanned 1 week before the stimulation and 1 week after it. The electrical stimulation was centered in the ventral striatum bilaterally. The results were obtained comparing the pre- and post-PET scans showing a significant increased metabolism in the NAcc, Amygdala, DLPFC, DMPFC and ACC. Additionally a decreased metabolism in each of the VLPFC, VMPFC, Dorsal Caudate and Thalamus was also observed. These results partially disagree with the hyperactivation pattern observed in prefrontal areas and hypoactivation of subcortical areas in depressed and highly anhedonic participants. Furthermore the authors of the study reported some immediate clinical effects of the stimulation in two of the participants of the study. These patients manifested 60 s after the stimulation their willingness to engage in exploratory pleasurable behaviors (e.g. visiting a monument and taking up bowling again) that contrasted with the severe lack of motivation during their depressive episodes. The authors highlighted the important role of the NAcc in reward seeking behaviors.

The described pattern of hyperactivation of prefrontal areas and hypoactivation of subcortical areas in relation to reward deficits has also been observed in a study comparing two different groups of healthy and anhedonic-depressed individuals during an emotion regulation paradigm in response to positive, neutral and negative images [74]. In this study, participants were told to use cognitive appraisal to enhance or suppress their emotional responses elicited by visual standardized stimuli. The authors hypothesized that this fronto-striatal network related to reward processing was also the area responsible for positive emotion regulation, and therefore anhedonia might reflect an inability to sustain positive affect over time. At the
neural level this impairment would be manifested in a difficulty to maintain the activation of the NAcc during the task, specifically in the condition of enhancing the emotional response in front of positive stimuli. The results confirmed the authors’ predictions and anhedonic participants failed to sustain positive affect over time, reflecting a hypoactive fronto-striatal network that lead to abnormalities in reward processing and a general reduction in positive affect [74].

Interestingly, Pizzagalli and cols. [75] published for first time an fMRI study in which depressed-anhedonic individuals were presented with the Monetary Incentive Delay Task. This task is able to segregate the anticipatory and consummatory phases of reward processing, by first presenting a cue informing about the potential of receiving reward (monetary gain), punishment (monetary loss) or no-reward (no-incentive condition) and then later delivering the outcome (separated by a variable interval needed to allow for proper reconstruction of the BOLD response). The main results showed that depressed-anhedonic individuals displayed a decreased left NAcc activation when processing a positive outcome, during the consummation phase of reward processing. The authors claimed this finding could indicate a more primary deficit in hedonic coding. However no significant differences regarding reward anticipation were found in this study, with basal ganglia activations in this condition equal for both depressed and control participants. The authors also reported a bilateral reduction in the caudate nucleus for the depressed-anhedonic individuals that correlated with anhedonia severity scores. This result replicated a former study conducted with healthy high anhedonic participants previously mentioned [72].

Using the same Monetary Incentive task, the same research group conducted a follow-up study with healthy participants [80]. In this case different neuroimaging techniques were used (combining resting EEG frequency analysis, fMRI and volumetric techniques). Their results corroborated decreased NAcc responses to rewards and a reduction in NAcc volume was also found in accordance with the study of Harvey et al. [72]. This decrement during reward outcome processing lead the authors to interpret again that the differences in anhedonia were centered on the consummatory phase of reward processing, although findings in other studies using the same task defended the opposite hypothesis [85].

In a more recent study, Robinson and cols. [76] centered their aims on studying learning in depression. Although the focus of their research was depression and its cognitive and affective biases, these results are also relevant for a more thorough understanding of anhedonia symptomology and its relation with the BRS. Thirteen MDD patients and a control group were scanned while performing a reversal learning task. In each trial of the task, participants were presented with two squares, one of which was highlighted with a black border. One of the stimuli was associated with a reward and the other with a punishment. Participants were endeavored to predict whether the highlighted stimulus was related with a reward or a punishment. The trials were grouped in different mini-blocs (i.e. the rewarded stimuli was consecutively the same during some trials ranging from 4 to 6 correct responses in a row) including a variable number of reversal trials (changes in the rewarded stimuli). These reversal contingencies were marked with an unexpected reward or punishment
that was interspersed along the task. The analysis of the hemodynamic signal during
these trials revealed no differences between groups during unexpected punishments.
On the contrary, on unexpected rewards depressed individuals displayed diminished
right putamen activation. The authors believed that this hypoactivation may be
related to the impaired ability to derive pleasure from rewarding activities, i.e. the
anhedonidc symptoms, and also a reduced dopaminergic release.

Recently also, Dowd and Barch [77] published a study conducted with schizo-
phrenic patients. A Pavlovian Reward Prediction Paradigm was used where
participants had to choose between two stimuli predicting if it was going to lead to
a receipt of 75 cents or 0 cents. There was a cue-outcome association known by the
participant, so one of the stimuli was rewarded 75% of the time. This task permitted
the dissociation between reward anticipation and consummation, i.e. the anticipatory
and consummatory reward processing phases respectively. Interestingly, the results
showed little activation differences between clinical and control groups during both
experimental conditions. Those patients with higher anhedonia scores showed
reduced left ventral striatal and VMPFC activations during the anticipatory phase.
For the reward consummatory phase (outcome receipt), no differences were found
between groups. Thus, these results point out an equal capacity to experience reward
in the schizophrenic group (consummatory phase). However negative correlations
between anhedonia and some brain activations were found to be significant, for
example, higher physical anhedonia was associated with less ventral striatal and
VMPFC activation during the anticipation of rewards.

A new study recently published [30] was conducted with healthy participants
with no psychiatric history. In this case the authors examined brain responses and
effective connectivity of the mesolimbic reward system in relation to the anhedonia
trait. The authors used music pieces for the fMRI task, specifically 3 fragments of
likely familiar music and 3 fragments of likely unfamiliar pieces that had been used
in previous studies. The authors encountered that anhedonia had an impact in the
reactivity and connectivity of the mesolimbic and paralimbic structures involved in
reward processing. More precisely, the anhedonia trait was negatively correlated
with activations of NAcc, basal forebrain and hypothalamus. Other areas related to
the processing of salient emotional stimuli were also hypoactive in higher
anhedonic individuals, as for example the OFC cortex and anterior insula.

In summary, the present review of neuroimaging studies points out a clear
influence of anhedonia in the activation of several regions in the BRS network.
Although the results might appear contradictory in some cases, it is clear that this
research approach, studying the activation of this neural network involved in reward
processing, can help to understand the specific impairments observed in anhedonia
and in the different hedonic and motivational reward components. Further studies
are needed with carefully selected and larger samples of clinical and sub-clinical
populations and using more advanced and fine-grained behavioral tasks that permit
a clear dissociation of the different reward components. One of the main problems
of the previous studies is that different paradigms have been used, for example,
autobiographical events, viewing pictures, receiving performance feedback, differ-
ent rewards with time-pressure constraints, decision making, etc. An effort is needed
to use systematic well-validated experimental paradigms in order to firmly draw conclusions on the effects of depression and anhedonia on reward dysregulation.

## 11.6 Anhedonia Reward and Motivation

Interestingly to our aim, recent work in experimental economics [86] and decision making [87] suggests that there are large inter-individual differences with regard to the way we deal with rewards and punishments of different magnitudes in certain situations. Indeed, individual differences in the capacity to experience pleasure could be linked to a possible dysfunction in the reward and motivation systems as has been proposed for depression [71, 75, 88, 89]. However, unravelling which aspect of reward processing is altered in anhedonia is a current concern. The dissociation between consummatory and anticipatory processes suggests a specific deficit in keeping internal representations of possible rewarding experiences active, and therefore reducing the possibilities to correctly direct actions. Indeed, this notion is consistent with a recent neuroimaging study [74] showing that depression may not be solely due to a tonic reduction in the capacity to experience pleasure, but to the inability to sustain positive affect and reward responsiveness over time. Concurrent with this idea, in an excellent review, Treadway and Zald [89] have recently argued for the distinction between “consummatory anhedonia” (deficits in the hedonic responses) and “motivational anhedonia” (diminished motivation to pursue hedonic responses), which is based on the previous conceptualization of “liking” and “wanting” processes in reward processing.

This dissociation observed between reward consumption and the changes observed in motivational approach-behavior could help to understand the origin of the individual differences observed in anhedonia in sub-clinical populations. In this sense anhedonics usually show diminished motivation to engage in goal-directed behaviors and to use information about potentially rewarding events. This distinction is critical to better understand individual differences regarding hedonic experiences in clinical populations. Previous studies with schizophrenic patients suggested that while the experience to engaging in enjoyable activities seems to be more or less preserved [25, 90], these patients report less anticipatory pleasure in goal-directed activities that could potentially allow them to obtain desired rewarding experiences [91]. Moreover, two recent clinical studies of anhedonia and depression in a college student population primarily reflect low levels of anticipation of reward and a tendency to accurately estimate their enjoyment of future rewards [92, 93]. Moreover, several studies in depressed patients have shown relatively normal self-rated experience of encounters with pleasurable stimuli suggesting a preserved hedonic capacity to experience a primary reinforcer (see for a review, [89]). For example, across four studies on the “sweet taste test”, which is one of the measures used for evaluating hedonic capacity, no differences were observed between depressed patients and matched control participants [94–97]. These findings give support to the idea that anhedonia in clinical settings might be a consequence of deficits in motivation and anticipatory but not consummatory pleasure.
Besides, reward and learning brain systems are inherently interconnected (see above, Fig. 11.1a), which could explain the differences in motivation approach-behavior patterns and decision making observed in anhedonics and the development of different learning patterns across life. Previous studies have shown that depressed patients tend to focus on negative rather than positive aspects of their lives \[98, 99\] and that they have experienced less positive reinforcements along their life \[100\]. These results suggest that anhedonics might show increased attention in risky situations (that could potentially result in a punishment) and less expectation of receiving positive feedback. In line with classic theories of depression \[101\], anhedonics might have a lower propensity to perceive reality in an optimistic fashion and consequently avoid occasions that could potentially be highly positive and pleasurable. Indeed a very prominent cognitive theory of depression emphasizes the role of dysfunctional negative schemas or attitudes in biasing the processing of feedback information \[102\].

In this concern and in agreement with the importance of anhedonia in taking risks or motivational-approach behaviors, a recent study demonstrated that schizophrenic patients with high levels of anhedonia are less prone to explore uncertain environments, probably due to their prior negative expectations and reduced sensitivity to assess opportunities that could be better than expected \[103\]. Moreover, in examining the effects of negative feedback on subsequent performance it has been shown that depressed and anhedonic participants show abnormal responses to negative feedback \[104–107\] and had attenuated trial-by-trial changes in reaction after reward and punishment trials \[108\]. These attenuated adjustments observed in patients or anhedonic participants might be associated either to inefficiency in using feedback knowledge to monitor their performance or alternatively to an inherent lack of motivation to obtain potential positive rewards with the consequence of not experimenting the same drive to improve their performance along the task.

Importantly, for the present review, while the studies presented before in which metabolic or hemodynamic brain techniques (PET or fMRI) have been used to unravel the emotional impact of reward in clinical and sub-clinical anhedonic populations, these studies are certainly blind to the temporal dynamics of anticipatory and consummatory brain activity. Other neuroimaging techniques as for example, Event-related brain potentials or Time-frequency analysis of electroencephalographic activity are more suited.

### 11.7 Electrophysiological Responses Associated to Reward Processing

In humans, electrophysiological (Event-Related Brain Potentials, ERPs) studies have identified several components that specifically indicate the processing of negative outcomes, such as negative feedback, monetary loss, or the detection of performance errors, as well as positive outcomes, such as monetary gains and positive feedback. With regard to negative outcomes, a negative deflection over frontocentral
scalp locations (see Fig. 11.3a), known as Feedback Related Negativity (FRN) [58] or Medial Frontal Negativity (MFN) [112], has been described peaking at 250–300 ms after the presentation of a negative feedback or monetary losses in a gambling task (see for a recent review, [116]). The neural sources of this component have been located in the anterior and the posterior cingulate cortex [114]. The dynamics of the FRN have been explained using the reinforcement learning theory (RL theory; [58, 117]), which proposes that when an action produces a worse than expected consequence (e.g. an error in a selection task or a loss in a gambling task) there is a decrease in the mesencephalic midbrain dopaminergic activity that is transmitted to the anterior cingulate cortex (ACC) through the mesocortical pathway (see for a recent review, [118]). Thus the FRN has been related to midbrain dopaminergic modulations of a reinforcement learning system that evaluates events to guide

Fig. 11.3  (a) Illustration of the monetary gambling paradigm used to evaluate reward processing in several ERPs studies from our laboratory [109–111] (see previous figure for an explanation). (b) ERPs associated to monetary gains (black line) and monetary losses (red line) at a frontal-central electrode location (Fz). Notice the increase of the negativity in monetary loses compared to gains observed at about 250 ms, which is called Feedback Related Negativity (FRN) [58, 112, 113]. The topographical scalp distribution of the FRN (blue means increase of negative voltage in μV and red represents positive voltage values) is depicted, showing a clear fronto-central distribution of the FRN which is compatible with the location of the component near the VMPFC/ACC [114]. (c) Time- Frequency oscillatory analysis resulting from the contrast of monetary gains vs. monetary loses. Loses show a clear increase of power (blue color scale) between 4 and 6 Hz (theta oscillatory band), while gains presented an increase in oscillatory activity between 20 and 30 Hz (hot color scale, which is in the range of Beta-Gamma component [110, 115]). It is mentioned in the text that this Theta oscillatory increase as associated with the processing of monetary losses or negative feedbacks and that Beta-Gamma oscillatory increases are associated with monetary gains or the processing of positive feedback.

[54x201]scalp locations (see Fig. 11.3a), known as Feedback Related Negativity (FRN) [58] or Medial Frontal Negativity (MFN) [112], has been described peaking at 250–300 ms after the presentation of a negative feedback or monetary losses in a gambling task (see for a recent review, [116]). The neural sources of this component have been located in the anterior and the posterior cingulate cortex [114]. The dynamics of the FRN have been explained using the reinforcement learning theory (RL theory; [58, 117]), which proposes that when an action produces a worse than expected consequence (e.g. an error in a selection task or a loss in a gambling task) there is a decrease in the mesencephalic midbrain dopaminergic activity that is transmitted to the anterior cingulate cortex (ACC) through the mesocortical pathway (see for a recent review, [118]). Thus the FRN has been related to midbrain dopaminergic modulations of a reinforcement learning system that evaluates events to guide
reward-seeking behavior. This ERP component is thought to reflect the degree of negative prediction error, a signature of when events are worse than expected [58, 119]. Accordingly, these dopaminergic reinforcement learning signals in the ACC might help the organism to cope with potential cognitive conflicts arising from previous expectations and unexpected outcomes. Thus, ACC might enhance action monitoring and control processes that will help to improve task performance and to increase the adjustment of further decision making processes [58, 83, 84].

It is important to bear in mind that the FRN component has been consistently associated to medial frontal theta oscillatory activity (4–8 Hz) [109, 120–122]. It has been proposed that increases of medial-frontal theta component may represent a general top-down mechanism operating over expectation violation and behavioral adaption in order to improve performance and learning [120, 123–127]. Consistent with this idea many studies have shown the involvement of medial-frontal theta oscillations in error monitoring [115, 121, 128], processing of negative experiences [110, 129], rule/expectation violations [123, 125] and in the computation of prediction errors in service of behavioral adaption and learning [126, 127, 129].

Finally, recent studies from our laboratory and others have found a power enhancement of high frequency beta-gamma (27–32 Hz, 270–310 ms) oscillatory activity associated to the processing of positive feedback or outcomes [109, 121, 126, 129, 130] (see Fig. 11.3c), sensitive to the reward magnitude [121], and probability [129]. For example, in a recent study we showed that unexpected large monetary gains elicited a larger increase in the power of this beta-gamma oscillatory component [130]. In humans, consummatory behavior (drinking) was associated with an increase in cortical EEG beta power [131]. Animal studies have also observed an increase of beta activity in the striatum after reward delivery [132]. These studies together suggest that beta-gamma oscillatory activity might be a potential neural signature of consummatory reward processing. Due to the large network involved in the processing of reward and positive affect (see Fig. 11.2b), our group has proposed that beta activity orchestrates reward processing through such aforementioned fronto-striatal circuits [110, 130].

In summary, crucially for the evaluation of the neural dynamics of reward processing, two electrophysiological components have been well delineated during the last decade: (i) the Feedback-related negativity and its underlying Theta-oscillatory activity which has been related to the processing of negative outcomes (e.g., monetary losses) and unexpected negative consequences of our actions; and (ii) Beta-Gamma oscillatory activity related to the processing of positive feedback events related to our actions (e.g., monetary gains).

11.8 Electrophysiological Studies Associated to Reward Processing and Anhedonia

Recently in our lab we evaluated the neurophysiological dynamics of reward processing using EEG in a carefully selected group of highly anhedonic participants (using the PAS physical anhedonia scale) [111]. From a large group of university
participants, we selected two groups of extreme PAS scores: (i) the anhedonic group (PAS mean anhedonia score, 26.0 ± 3.2 (standard deviation)) and (ii) a non-anhedonic group (highly hedonic participants; PAS mean value of 3.4 ± 1.2). Notice that the anhedonic group show high values of the anhedonia trait considering that in major depression samples, normal values of the PAS scale are close to 37 (see for example, [133]). In our study, we applied the previous ERP methodology in a very simple gambling task (based on [48, 121]; see Fig. 11.3a for the design), in which participants were requested to choose the amount of money they wanted to gamble in each trial (either choosing a small amount, 5 euro cents or a large amount, 25 euro cents). Participants randomly received positive or negative feedback about their decisions, informing them if they had won or lost the amount of money they had gambled. The instructions of the task requested participants to make an effort to gain as much money as possible, however the monetary gains and losses were assigned randomly. Thus, no rule or pattern was able to be discovered in order to increase the amount of monetary gains; both groups received equal amount of monetary gains and losses and gained equal amount of money. Using this task, we were able to evaluate two important aspects using the previous electrophysiological signature detailed in the previous section: (i) if the emotional impact of monetary gains and losses was similar across groups (consummatory aspects), and (ii) to which degree, depending on the expectations generated by participants during the task, the ERP and Time-Frequency modulations observed could reflect different anticipatory or motivational-approach patterns to the current task.

One of the most important results of this study was the lack of electrophysiological differences observed in the consummatory responses in anhedonics in reward processing for monetary gains and losses. In Fig. 11.4a we can for example observe the ERP pattern for both groups and for the monetary gains and monetary losses (when the feedback they received informed them that they had lost or won 25 euro cents). Notice the large similarity in both cases, for the Feedback related component (FRN) as well as for the increased positive component (P300) associated to the processing of monetary gains. In a similar fashion, no differences were observed for the positive-feedback related oscillatory component, the beta-band, in both groups (see Fig. 11.4b, where we depicted the difference between gains and losses in both groups). These results suggest normal processing of positive and negative outcomes in a monetary gambling task for highly anhedonic participants and concur with previous findings of intact hedonic responses in anhedonic and depressive patients [95, 134, 135]. The lack of differences in the FRN in our study for anhedonic participants somehow contrast with previous studies using similar ERP components in depression. For example, an association was encountered between the amplitude of the FRN and depression and stress scores in a recent study using a large group of undergraduate students [136]. However, the opposite results have been observed in others studies [137, 138]. In the study by Foti and Hajcak [136] the authors used a gambling task and it was observed that the amplitude of a principal component associated to the FRN (using the difference of non-reward vs. reward trials) was inversely related to depression and stress scores (the correlation value was relatively small, r = .23). The authors suggested that the FRN reduction in response to monetary loses in individuals with increased levels of depression could be driven by...
Fig. 11.4  (a) Grand average ERPs at frontal electrodes for Anhedonic and non-Anhedonic individuals regarding large monetary rewards and large monetary losses. Notice the similarity in both groups of the FRN component, indexing the evaluation of negative outcomes and the subsequent positive component (P300), associated to the processing of monetary gains (From Ref. [111]). (b) Time-frequency analysis showing the power change with respect to baseline between large monetary gain and large monetary loss at frontal electrodes. No differences between both groups were observed for the positive feedback-related oscillatory component in the beta-band (28–32 Hz, highlighted by the dotted square). (c) Evolution of the risky choices (choosing 25 euro cents instead of 5) across the whole task. Each bin is composed of 40 trials (mean proportion of choosing 25 in that particular bin). The soft grey line corresponds to the chance level ($p=0.5$). The asterisks represent a serial one-sample t-test in which the 25/5 proportion was significantly above the chance level expected. Notice that a clear tendency exists in the non-Anhedonic group to show significant increases of risk along the task, when compared to the Anhedonic group.
biased expectations for negative outcomes. In any case, although anhedonia is a core symptom of depression, it is difficult to compare our results with the ones obtained in clinical studies with depressive patients or in similar studies as the one from Foti and Hajcak, as other important factors affecting depression scores could be responsible for the differences observed in the FRN amplitude.

The most interesting aspect of this study is that we observed an unpredicted increase in theta-oscillatory activity after the processing of large gains only in the anhedonic group (see Fig. 11.5a, b). This is an interesting finding as the increase in theta-activity, as we explained above, has normally been reported exclusively for the processing of negative feedback, monetary losses, erroneous responses or the violation of current expectations (see [123], but not for monetary gains. Thus considering that this medial-frontal theta component has been observed also in relation to an increase in cognitive control and conflict detection [84, 124] as well as the computation of expectancy deviation of the predicted outcome of the current action [120, 123, 125, 139, 140], we interpreted this finding as a violation of negative expectations in anhedonic participants created across the task. In this sense, when a large gain or positive outcome is received in these participants it might elicit an internal conflict between prior negative expectations and the unexpected positive outcome, increasing cognitive control and showing as a corresponding increase in theta activity. What’s more, we found that this increase in the theta component was larger for monetary gains that were preceded by a prior large monetary gain. In this sense, receiving a large gain probably reduced the expectancy of sequentially receiving another large reward, and therefore increased the amount of conflict experienced (increase in theta) when receiving the large monetary gain in the subsequent trial. This interpretation is consistent with previous studies showing a tendency in depressive patients to create negative expectations about future events [98, 99]. In this
sense anhedonia could be related to the difficulty of sustaining positive expectations over time about the outcomes of current actions [74, 89].

More evidence of this negative bias in the anhedonic group was shown when the behavioral risk pattern was analyzed in this group. As it is shown in Fig. 11.4c, the group of anhedonic participants showed a reduced tendency to make risky choices (gambling the largest amount instead for the smaller one) during the course of the task. This less risky pattern in anhedonics might restrict the possibility of obtaining larger monetary gains. Indeed this behavioral pattern concurs very well with the results obtained from the psychometric assessment of the susceptibility to avoid possible negative events (evaluated using the BIS/BAS scales [141] and the Sensitivity to Punishment and Reward questionnaire, SPSRQ [142]). Anhedonic participants characterized themselves as strongly willing to avoid possible punishment and therefore have a marked behavioral tendency to choose non-risky patterns. Overall these results are coherent with the negative bias hypothesis in anhedonics about future rewards and their impediment to sustain positive expectations about the results of their own actions. These results also agree with previous findings showing that anhedonia and depression are associated to certain incapacity to appropriately use feedback knowledge to monitor and improve their own performance [108]. Similarly, depressive individuals presume that negative outcomes are more likely for their actions in more uncertain situations [98, 99, 102] and might be less prone to perceive reality in an optimistic way and consequently avoid occasions that could potentially be highly positive and rewarding [101, 102].

In this regard and in agreement with the importance of anhedonia in risk-taking, a recent study demonstrated that schizophrenic patients with high levels of anhedonia are less prone to explore uncertain environments, probably due to their prior negative expectations and reduced sensitivity to assess opportunities that could be better than expected [103]. In the same vein it has been demonstrated that unmediated depressed individuals display an impaired tendency to modulate behavior as a function of previous rewards indicating a lack of capacity to integrate a reinforcement history over time [143].

Interestingly, one of the first psychophysiological studies of the anhedonia trait [144] used slow-cortical related potentials and heart-rate responses to investigate the effects of anhedonia (measured using the PAS scale) during the anticipation of neutral (e.g., a folding chair) or emotionally interesting stimuli (e.g., a sexual-related slides). In this paradigm, an auditory warning stimuli (6 s duration) informed participants about the emotional category (neutral or high-interest) of the color slide that was about to appear. Normally, high interest events elicit a marked acceleration of heart rate and an increase in the amplitude of the Contingent Negative Variation (CNV), which is a slow frequency cortical ERP component. The CNV has been related to the amount of motivation, preparation or attentional anticipation to the appearance of the next informative stimuli (or emotional feedback). The most interesting finding was that anhedonic participants (with a mean PAS score of 27) showed diminished amplitude of the CNV in the high interest emotional condition when compared to the non-anhedonic or control participants (mean PAS score of 10). Indeed, no difference was observed
in the CNV amplitude between neutral and high-interest emotional anticipation in the anhedonic group while waiting for the presentation of the stimuli. Thus this study seems to be in agreement with the results presented above and point out the possibility that anhedonia reflects the inability or lack of desire to approach or anticipate pleasurable activities rather than consummatory pleasure (see [95, 134, 135, 145]). Overall these results suggest that once in a pleasurable situation, anhedonic individuals might experience as much pleasure from the situation as non-anhedonic individuals.

Finally, results from Padrão and co-workers [111] are also in concurrence with a recent study in which patients with MDD showed motivational and decision-making deficits evidenced using a new experimental task (Effort Expenditure for Rewards Task, EEfRT) that evaluated motivation and effort-based decision making [133]. MDD patients showed less willingness to expend effort with the aim of gaining larger amount of money when compared to healthy controls (see also [146], for similar results in healthy anhedonic participants). These results fit well with the risky avoidance pattern shown in Fig. 11.4c in our anhedonic participants and points to the crucial involvement of anticipatory and motivation reward-related processes in anhedonia and MDD. Similar results were presented by Sherdell and collaborators [93] and showed that MDD patients did not differ in their “liking” ratings of humorous and non-humorous cartoons but differed in the amount of effort invested in obtaining certain rewards and therefore on their anticipatory pleasure.

In relation to the hypothesis of effort and motivation deficits in anhedonics, early ERP studies were focused on the study of subtle cognitive and attentional deficits in highly anhedonic participants. For example, Miller et al. [147] used an auditory (tone) discrimination task and found that anhedonia was related to the difficulty in correctly using memory templates for correct discrimination. In this study, the authors observed enhanced amplitude of the N200 component in anhedonic participants suggesting a difficulty to habituate to previous presented auditory information [see for a replication, [148]]. The authors argued that anhedonics processed each tone as novel events without showing repetition or familiarity effects. These results were somehow in agreement with existing interpretations at that moment regarding the cognitive deficits observed in schizophrenia, as for example, (i) perceptual gating problems, (ii) difficulty in forming sets of memory templates, (iii) difficulty in habituating to sensory stimuli and (iv) difficulty in the execution of automatic processes pertinent to sensory stimuli (see [148]).

Moreover, several ERP studies proposed that anhedonic participants show problems correctly allocating their attentional resources to simultaneous tasks (see [149]; see also [150–152]). In this sense, these studies concur with reductions of effortful cognitive processing in anhedonic participants [133, 146]. In agreement with this, a systematic trend has been observed in anhedonic participants that shows a reduction in the amplitude of the endogenous ERP component P300, which has been associated to effortful-attentional and decision-making processes [153] as well as contextual memory updating processes (see for example, [144, 147, 149, 150, 152, 154, 155]). However, this result is not completely consistent...
in the literature and several studies have not encountered the reduction in the amplitude of P300 in anhedonic participants [111, 148, 156]. A possible explanation for the differences between these studies could be related to the different amount of effort and attentional control across the tasks, the effect being larger in those studies in which the task needed greater amounts of attentional resources due to complexity [147, 150, 157]. Further studies are needed to test the hypothesis of an overall deficit of attentional location in anhedonic participants, evaluating more systematically different levels of complexity and effort in different cognitive tasks as well as more specific evaluations of the different neural attention networks that have been recently proposed (see [158]). Finally, previous ERP studies [157, 159] have also shown evidence of intact early stimulus information processing (using stimulus-related exogenous ERP components, for example, the N1 and P2 components in auditory processing or the N2 in auditory oddball tasks) in anhedonic participants. These studies ruled out the possible influence of anhedonia in early information processing stages (but see for contradictory evidence in the auditory domain, [148, 154]).

Overall, the ERP studies reviewed above tend to suggest an important role of anhedonia in modulating reward anticipation and motivation. One interesting line of research, and following the early findings of Simons et al. [144] using slow ERP components (CNV), might be to investigate more carefully the temporal and time-frequency EEG dynamics of anticipatory periods during reward or learning tasks. In this regard, in two recent new studies of our group, we observed that a slow ERP component, the Stimulus Preceding Negativity (SPN; see for a review, [160]), could be used to track on-line the amount of anticipation built-up while waiting for a desired reward [161] as well as evaluating the temporal dynamics of the learning process in a trial-by-trial associative learning task [162]. In the study of Fuentemilla and co-workers [161], they showed a clear increase in the amplitude of this slow-ERP component, the SPN, in situations in which the appearance of a highly desired reward was very unlikely, compared to other outcomes that were more probable and equally desirable. Thus using this paradigm, we could evaluate to what extent, very unexpected but highly desired rewards, could show differences between anhedonics and non-anhedonics participants in anticipatory reward phases. In the second study, we investigated if this component, the SPN, could be used as a possible correlate of information expectation during associative learning. The results of this study showed that the SPN offers a reliable ERP component to measure on-line the cognitive processes that take place while waiting for forthcoming feedback, which might be crucial for successful learning. In both cases, the benefit of the ERPs in relation to its temporal sensitivity can clearly help to understand the amount of attention and emotional impact of anhedonic participants during anticipatory-reward phases. We believe that using this strategy, which is very well suited to ERPs, might help to understand better the impact of anhedonia in the temporal dynamics of the anticipatory phases of reward learning and reward processing.
11.9 Conclusions and Research Agenda

The studies reviewed here show clearly that a thorough understanding of anhedonia, traditionally seen as a unified concept, and its psychopathological implications require a distinction between consummatory and anticipatory reward components (see also [89]). From the electrophysiological data presented in relation to reward processing and previous behavioral studies reviewed, anhedonia seems to be characterized by a tendency to create negative expectations towards upcoming reward events, which might be reflected in an elevated avoidance of risky decisions, increased sensitivity to negative events and less capacity to appropriately integrate feedback knowledge and past learning experiences to increase the chances of obtaining positive outcomes [108, 146]. Importantly, no electrophysiological differences were observed due to anhedonia in reward processing of positive or negative outcomes which speaks in favor of preserved consummatory reward processing [111]. Therefore, anhedonic participants might have an intact hedonic capacity but an impairment in anticipating future positive outcome rewards that makes their engagement in pleasurable activities less likely. New research should be devoted to properly studying the implication of the multifaceted construct of anhedonia and its clinical symptoms in distinct reward-based subcomponents, for example the evaluation of the hedonic experience (pleasure effects), affective valuation of the possible rewards, anticipatory and motivational processes and finally the integration of these processes in actual decision-making. We believe that the incorporation of more fine-grained and sophisticated temporally sensitive techniques such as the ERPs will help in future to understand the neurobiological basis of reward-related dysfunctions and will allow the design of more effective treatments and preventive interventions.

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References


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