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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 (separated by "-")	Anhedonia - Depression - Reward processing - Feedback processing - Learning - Feedback-related negativity - Medial-frontal theta oscillatory activity - Beta–gamma oscillatory - Motivation

Chapter 11
Electrophysiological Signatures of Reward Processing in Anhedonia

Aida Mallorquí, Gonçalo Padrao, and Antoni Rodriguez-Fornells

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/

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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.

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Abbreviations

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

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]).

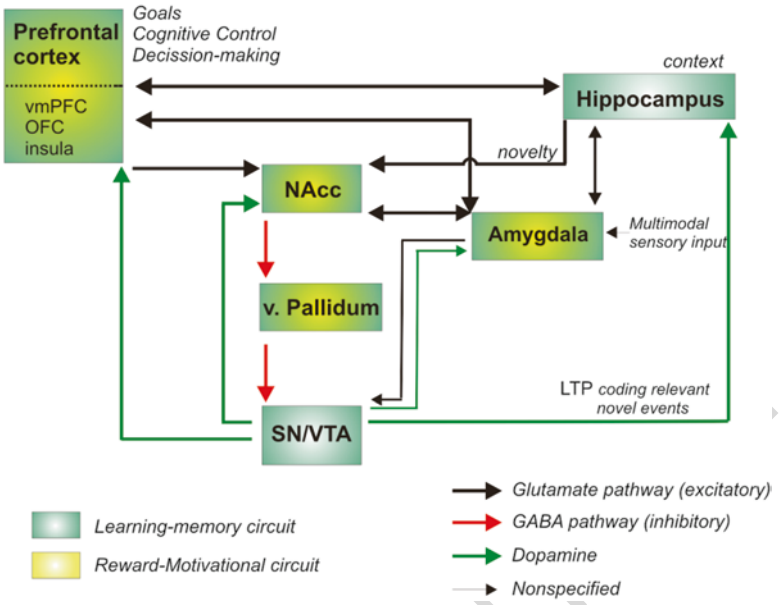

Fig. 11.1 Schematic representation of the principal structures involved in reward processing, their interconnectivity and principal neurotransmitter systems. The diagram shows the interaction between the reward processing networks with the regions involved both in learning and memory processes. *Green boxes* highlight the hippocampal-midbrain (VTA) learning-memory circuit described by Lisman and Grace [40]. The reward-motivational system has been adapted partially from Kelley [47] (*green-yellow boxes*) [Adapted from Ref. [34], *LTP* long-term potentiation, *v* ventral]

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,

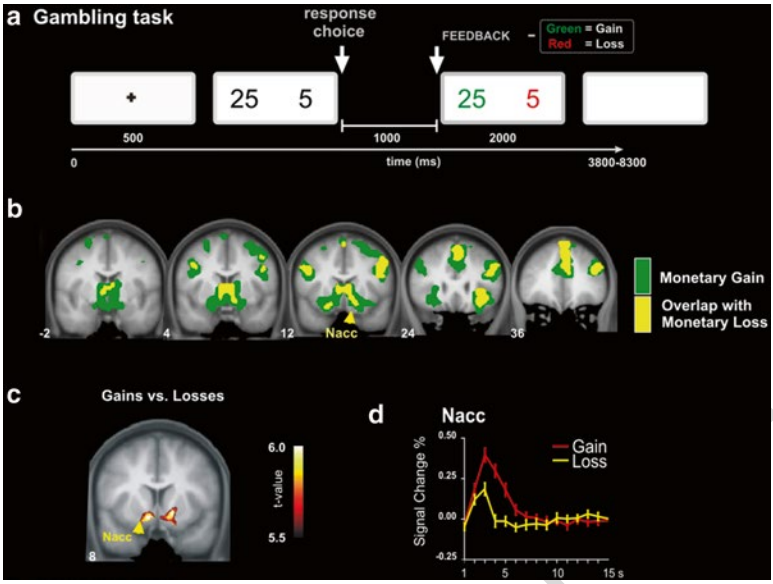

Fig. 11.2 (**a**) Sequence of stimulus and response events in the gambling task used in our laboratory for fMRI reward gambling studies [48–50]. After a warning signal, a pair or numbers ([5, 25] or [5, 25]) is presented and participants are forced to select one of the numbers by pressing the corresponding 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]

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.

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

t1.1 **Table 11.1** Summary of the neuroimaging studies related to reward processing and anhedonia reviewed in the text

Study	Year	Sample	Technique	Anhedonia measure	Task	Activated regions in anhedonia
Mitterschiffthaler et al. [70]	2003	7 female depressed patients	fMRI	FCPS	IAPS Picture Attentive Observation	Increased activation in frontal lobes, thalamus, basal ganglia and insula
Keedwell et al. [71]	2005	12 MDD patients	fMRI	FCPS	Mood Provocation Paradigm (using autobiographical memories)	VMPFC and Anterior Caudate (in front of + stimuli)
Harvey et al. [72]	2007	29 non-clinical adults	fMRI/VBM	PAS	Emotional Memory Task as covert emotional processing using IAPS stimuli	VMPFC activation (for + stimuli) and volumetric reduction in the Anterior Caudate
Schlaepfer et al. [73]	2008	3 resistant MDD patients	PET	Subject Verbal Report	No task. Deep Brain Stimulation in NAcc (ventral striatum)	NAcc, Amygdala, DLPFC, DMPFC increased metabolism. Ventral and VLPFC decreased metabolism.
Heller et al. [74]	2009	27 MDD patients	fMRI	None	Emotion Regulation Paradigm by cognitive appraisal using IAPS stimuli	NAcc decreased activation across the task in front of positive stimuli. Reduced connectivity between NAcc and Left Middle Frontal Gyrus

t1.26 t1.27 t1.28 t1.29	Pizzagalli et al. [75]	2009	30 MDD patients	fMRI/VBM	BDI items referred to anhedonia	Monetary Incentive Delay Task	Left NAcc decreased activation when processing positive outcomes. Reduced Caudate volume bilaterally
t1.30 t1.31 t1.32	Wacker et al. [31]	2009	33 non-clinical adults	Resting EEG/ fMRI/ Volumetry	MASQ-AD	Monetary Incentive Delay Task	NAcc decreased activation in front of + stimuli. NAcc volume reduction
t1.33 t1.34 t1.35	Robinson et al. [76]	2012	13 MDD patients	fMRI	None	Reversal Learning Task	Right Putamen activation attenuated on unexpected rewards
t1.36 t1.37 t1.38 t1.39	Dowd et al. [77]	2012	29 patients with schizophrenia or schizoaffective disorders	fMRI	PAS and SAS	Pavlovian Reward Prediction Task	
t1.40 t1.41 t1.42 t1.43 t1.44 t1.45 t1.46	Keller et al. [30]	2013	21 non-clinical adults	fMRI/Effective connectivity	PAS, SAS and MASQ-AD	Listening to familiar and unfamiliar musical pieces	Reduced reactivity and connectivity of the mesolimbic reward system. Decreased activation in NAcc, basal forebrain, hypothalamus, OFC and anterior insula

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 anhedodnic symptoms, and also a reduced dopaminergic release.

Recently also, Dowd and Barch [77] published a study conducted with schizophrenic 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, different 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

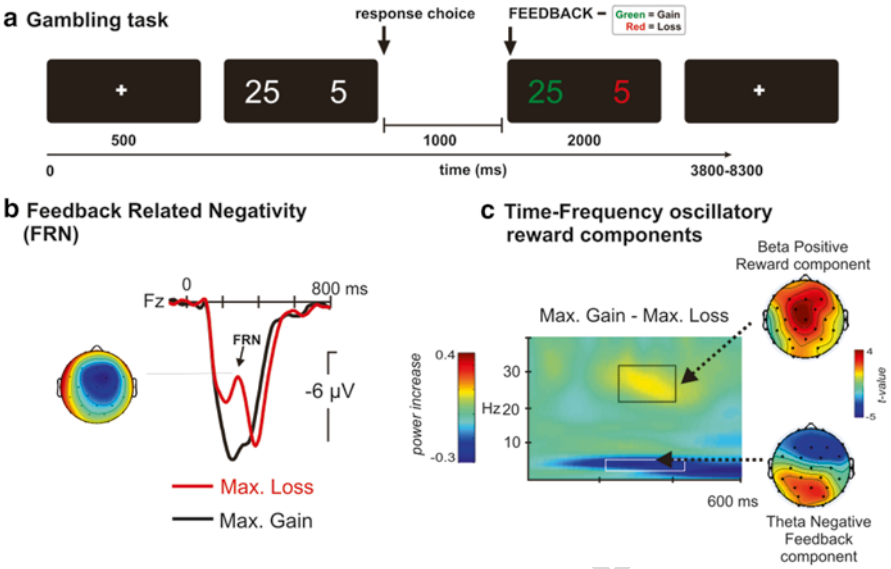

Fig. 11.3 (**a**) Illustration of the monetary gambling paradigm used to evaluate reward processing in several ERPs studies from our laboratory [109–111] (see previous figure for an explanation). (**b**) ERPs associated to monetary gains (*black line*) and monetary losses (*red line*) at a frontal-central 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]. [AU2] IThe 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

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

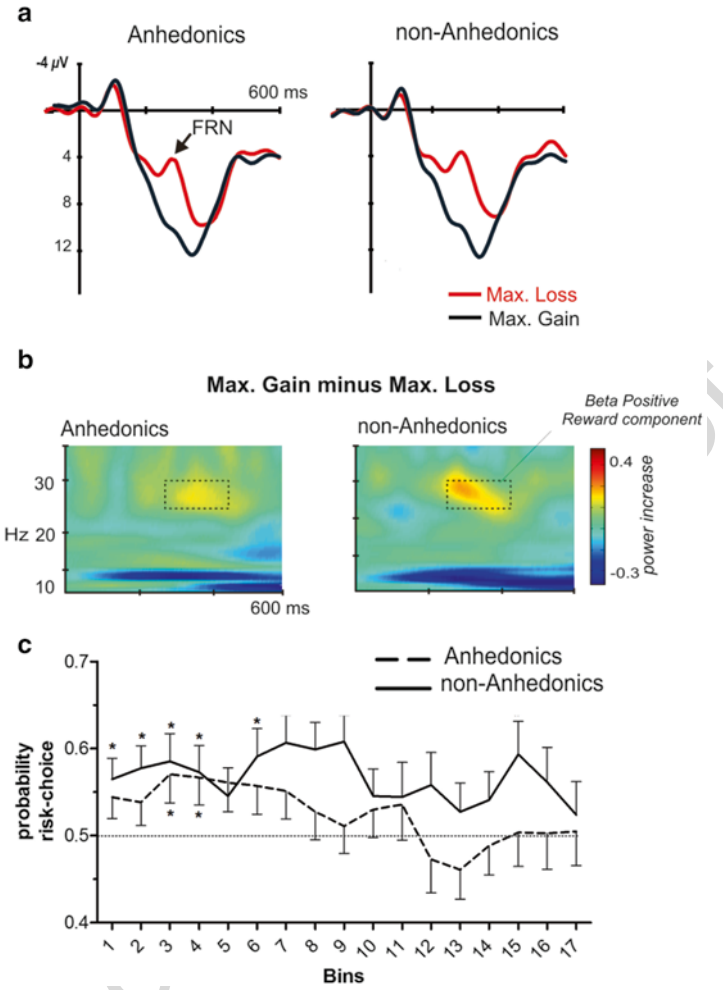

Fig. 11.4 (**a**) Grand average ERPs at frontal electrodes for Anhedonic and non-Anhedonic individuals regarding large monetary rewards and large monetary losses. Notice the similarity in both groups of the FRN component, indexing the evaluation of negative outcomes and the subsequent positive component (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

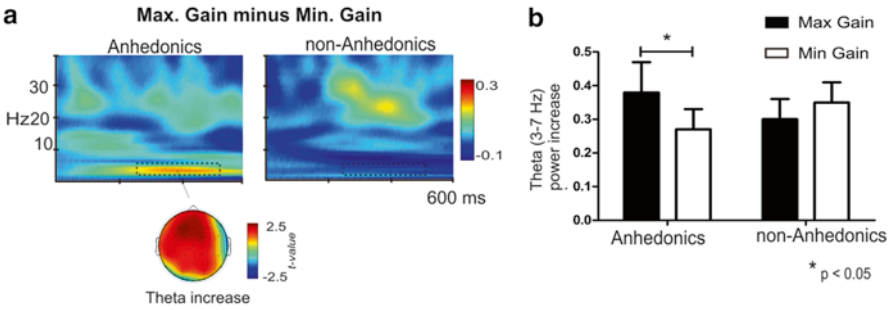

Fig. 11.5 (**a**) Medial-frontal theta oscillatory activity for the difference Maximum or large Gain minus Minimum or small Gains in Anhedonic and non-Anhedonic groups at frontal electrodes and the topographical distribution of the theta-related activity (3–7 Hz) [111]. Notice that a theta increase was observed for the Anhedonic group with a clear fronto-central scalp distribution. (**b**) Graphic representation (*t*-test comparison) of the difference between Maximum Gains and Minimum Gains in both groups. The figure highlights the increase of the theta band in the 250–450 ms time range for the Anhedonic group after receiving unexpected large monetary rewards (Max. Gain condition)

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 unmedicated 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) o 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 Padrao 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

[AU3]

1. Shankman SA, Nelson BD, Harrow M, Faull R. Does physical anhedonia play a role in depression? A 20-year longitudinal study. J Affect Disord. 2010;120(1–3):170–6.
2. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology. 2004;29(10):1765–81.
3. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol Psychiatry. 2005;57(4):319–27.
4. Berrios GE, Olivares JM. The anhedonias: a conceptual history. Hist Psychiatry. 1995;6:453–70.
5. Meehl P. Hedonic capacity: some conjectures. Bull Menninger Clin. 1975;39:297–307.
6. Loas G. Vulnerability to depression: a model centered on anhedonia. J Affect Disord. 1996;41(1):39–53.

7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Revised 4th ed. Washington, DC: American Psychiatric Association; 2000.
8. World Health Organization. The ICD-10 classification of mental and behavioral diseases. Geneva: WHO; 1992.
9. Foussias G, Remington G. Negative symptoms in schizophrenia: avolition and Occam's razor. Schizophr Bull. 2008;36(2):359–69.
10. Horan WP, Reise SP, Subotnik KL, Ventura J, Nuechterlein KH. The validity of psychosis proneness scales as vulnerability indicators in recent-onset schizophrenia patients. Schizophr Res. 2008;100(1–3):224–36.
11. Pelizza L, Ferrari A. Anhedonia in schizophrenia and major depression: state or trait? Ann Gen Psychiatry. 2009;8:22.
12. Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. Mol Psychiatry. 2011;16(6):604–19.
13. Bogdan R, Pizzagalli DA. The heritability of hedonic capacity and perceived stress: a twin study evaluation of candidate depressive phenotypes. Psychol Med. 2009;39(2):211–8.
14. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160(4):636–45.
15. Fawcett J, Clark DC, Scheftner WA, Gibbons RD. Assessing anhedonia in psychiatric patients. Arch Gen Psychiatry. 1983;40(1):79–84.
16. Clark DC, Fawcett J, Salazar-Grueso E, Fawcett E. Seven-month clinical outcome of anhedonic and normally hedonic depressed inpatients. Am J Psychiatry. 1984;141(10): 1216–20.
17. Herbener ES, Harrow M. The course of anhedonia during 10 years of schizophrenic illness. J Abnorm Psychol. 2002;111(2):237–48.
18. Herbener ES, Harrow M, Hill SK. Change in relationship between anhedonia and functional deficits over 20-year period in individuals with schizophrenia. Schizophr Res. 2005;75:97–105.
19. Blanchard JJ, Bellack AS, Mueser KT. Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. J Abnorm Psychol. 1994;103(4):719–28.
20. Katsanis J, Iacono WG, Beiser M, Lacey L. Clinical correlates of anhedonia and perceptual aberration in first-episode patients with schizophrenia and affective disorder. J Abnorm Psychol. 1992;101(1):184–91.
21. Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS. The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. Schizophr Bull. 2007;33(1):49–68.
22. Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. J Abnorm Psychol. 1976;85:374–82.
23. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995;167(1):99–103.
24. Franken IH, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). J Affect Disord. 2007;99(1–3):83–9.
25. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. Schizophr Res. 2007;93(1–3):253–60.
26. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J Res Pers Study. 2006;40:1086–102.
27. Leventhal AM, Chasson GS, Tapia E, Miller EK, Pettit JW. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. J Clin Psychol. 2006;62(12):1545–58.
28. Pizzagalli D, Sherwood R, Henriques J, Davidson R. Frontal brain asymmetry and reward responsiveness: a source-localization study. Psychol Sci. 2005;16(10):805–13.
29. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol. 1995;104(1):3–14.

30. Keller J, Young CB, Kelley E, Prater K, Levitin DJ, Menon V. Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. J Psychiatr Res. 2013;47(10):1319–28.
31. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage. 2009;46(1):327–37.
32. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008;199(3):457–80.
33. Kringelbach ML, Berridge KC. The functional neuroanatomy of pleasure and happiness. Discov Med. 2010;9(49):579–87.
34. Camara E, Rodriguez-Fornells A, Ye Z, Munte TF. Reward networks in the brain as captured by connectivity measures. Front Neurosci. 2009;3(3):350–62.
35. Berridge KC, Kringelbach ML. Building a neuroscience of pleasure and well-being. Psychol Well Being Theory Res Pract. 2011;1:3.
36. Panksepp J. Affective neuroscience: the foundations of human and animal emotions. New York: Oxford University Press; 1998.
37. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35(1):4–26.
38. Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci. 2002;22(9):3306–11.
39. Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiol Behav. 2005;86(5):773–95.
40. Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron. 2005;46(5):703–13.
41. McClure SM, York MK, Montague PR. The neural substrates of reward processing in humans: the modern role of FMRI. Neuroscientist. 2004;10(3):260–8.
42. Robbins TW, Everitt BJ. A role for mesencephalic dopamine in activation: commentary on Berridge (2006). Psychopharmacology (Berl). 2007;191(3):433–7.
43. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron. 2012;76(3):470–85.
44. Wise RA. Brain reward circuitry: insights from unsensed incentives. Neuron. 2002;36(2): 229–40.
45. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci. 2001;21(16):RC159.
46. Yacubian J, Glascher J, Schroeder K, Sommer T, Braus DF, Buchel C. Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. J Neurosci. 2006;26:9530–7.
47. Kelley AE. Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron. 2004;44(1):161–79.
48. Camara E, Rodriguez-Fornells A, Munte TF. Functional connectivity of reward processing in the brain. Front Hum Neurosci. 2009;1(19):1–14.
49. Camara E, Rodriguez-Fornells A, Munte TF. Microstructural brain differences predict functional hemodynamic responses in a reward processing task. J Neurosci. 2010;30(34):11398–402.
50. Camara E, Kramer U, Cunillera T, Marco-Pallares J, Cucurell D, Nager W, Mestres-Missé A, Bauer P, Schule R, Schols L, Tempelmann C, Rodriguez-Fornells A, Munte T. The effects of COMT (Val108/158Met) and DRD4 (SNP-521) dopamine genotypes on brain activations related to valence and magnitude of rewards. Cereb Cortex. 2010;20(8):1985–96.
51. Sescousse G, Caldu X, Segura B, Dreher JC. Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. Neurosci Biobehav Rev. 2013;37(4):681–96.
52. Tom SM, Fox CR, Trepel C, Poldrack RA. The neural basis of loss aversion in decision-making under risk. Science. 2007;315(5811):515–8.
53. Hariri AR, Brown SM, Williamson DE, Flory JD, de Wit H, Manuck SB. Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. J Neurosci. 2006;26(51):13213–7.

54. Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci. 2005;8(2):147–8.
55. Groenewegen HJ, Wright CI, Beijer AV, Voorn P. Convergence and segregation of ventral striatal inputs and outputs. Ann N Y Acad Sci. 1999;877:49–63.
56. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward leaning, or incentive salience? Brain Res Rev. 1998;28:309–69.
57. Goto Y, Grace AA. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci. 2005;8(6):805–12.
58. Holroyd CB, Coles MG. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychol Rev. 2002;109(4):679–709.
59. Berridge KC. Motivation concepts in behavioral neuroscience. Physiol Behav. 2004;81(2): 179–209.
60. Barbano MF, Cador M. Opioids for hedonic experience and dopamine to get ready for it. Psychopharmacology (Berl). 2007;191(3):497–506.
61. Burgdorf J, Panksepp J. The neurobiology of positive emotions. Neurosci Biobehav Rev. 2006;30:173–87.
62. Richardson DK, Reynolds SM, Cooper SJ, Berridge KC. Endogenous opioids are necessary for benzodiazepine palatability enhancement: naltrexone blocks diazepam-induced increase of sucrose-'liking'. Pharmacol Biochem Behav. 2005;81:657–63.
63. Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci. 2007;27:1594–605.
64. Zald DH, Zatorre RJ. Music. 2011. [AU4]
65. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 2012;35(1):68–77.
66. Toates FM. Motivational systems. Cambridge: Cambridge University Press; 1986. [AU5]
67. Salamone JD, Cousins MS, Bucher S. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. Behav Brain Res. 1994;65(2):221–9.
68. Venugopalan VV, Casey KF, O'Hara C, O'Loughlin J, Benkelfat C, Fellows LK, Leyton M. Acute phenylalanine/tyrosine depletion reduces motivation to smoke cigarettes across stages of addiction. Neuropsychopharmacology. 2011;36(12):2469–76.
69. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. J Neurosci. 2011;31(46):16597–602.
70. Mitterschiffthaler MT, Kumari V, Malhi GS, Brown RG, Giampietro VP, Brammer MJ, Suckling J, Poon L, Simmons A, Andrew C, Sharma T. Neural response to pleasant stimuli in anhedonia: an fMRI study. NeuroReport. 2003;14(2):177–82.
71. Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry. 2005;58(11):843–53.
72. Harvey PO, Pruessner J, Czechowska Y, Lepage M. Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry 2007;12(8):703, 767–03, 775.
73. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, Joe AY, Kreft M, Lenartz D, Sturm V. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology. 2008;33(2):368–77.
74. Heller AS, Johnstone T, Shankman AJ, Sharee NL, Peterson MJ, Kolden GG, Kalin NH, Davidson RJ. Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. Proc Natl Acad Sci U S A. 2009;106(52):22445–50.
75. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Losifescu DV, Rauch SL, Fava M. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166:702–10.
76. Robinson OJ, Cools R, Carlisi CO, Sahakian BJ, Drevets WC. Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. Am J Psychiatry. 2012;169(2):152–9.

77. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. PLoS One. 2012;7(5):e35622.
78. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry. 2010;67(10):902–11.
79. Morris RW, Vercammen A, Lenroot R, Moore L, Langton JM, Short B, Kulkarni J, Curtis J, O'Donnell M, Weickert CS, Weickert TW. Disambiguating ventral striatum fMRI-related BOLD signal during reward prediction in schizophrenia. Mol Psychiatry 2012;17(3):235, 280–35, 289.
80. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B. Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. Psychopharmacology (Berl). 2009;206(1):121–32.
81. Walter H, Heckers S, Kassubek J, Erk S, Frasch K, Abler B. Further evidence for aberrant prefrontal salience coding in schizophrenia. Front Behav Neurosci. 2010;3:62.
82. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, Rose EJ, Gold JM, Stein EA. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. Neuropsychopharmacology. 2010;35(12):2427–39.
83. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. Psychol Rev. 2001;108:624–52.
84. Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. Science. 2004;306(5695):443–7.
85. Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wustenberg T, Villringer A, Knutson B, Kienast T, Gallinat J, Wrase J, Heinz A. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology (Berl). 2006;187(2):222–8.
86. Glimcher PW. Indeterminacy in brain and behavior. Annu Rev Psychol. 2005;56:25–56.
87. Schall JD. Decision making. Curr Biol. 2005;15(1):R9–11.
88. Nestler EJ, Carlezon WA. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006;59(12):381–91.

[AU6]

89. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35(3):537–55.
90. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. Schizophr Bull. 2008;34(5):819–34.
91. Barch DM, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr Bull. 2010;36(5):919–34.
92. Chentsova-Dutton Y, Hanley K. The effects of anhedonia and depression on hedonic responses. Psychiatry Res. 2010;179(2):176–80.
93. Sherdell L, Waugh CE, Gotlib IH. Anticipatory pleasure predicts motivation for reward in major depression. J Abnorm Psychol. 2011;2.
94. Amsterdam JD, Settle RG, Doty RL, Abelman E, Winokur A. Taste and smell perception in depression. Biol Psychiatry. 1987;22(12):1481–5.
95. Berlin I, Givry-Steiner L, Lecrubier Y, Puech AJ. Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. Eur Psychiatry. 1998;13:303–9.
96. Dichter GS, Smoski MJ, Kampov-Polevoy AB, Gallop R, Garbutt JC. Unipolar depression does not moderate responses to the Sweet Taste Test. Depress Anxiety. 2010;27(9):859–63.
97. Kazes M, Danion JM, Grange D, Pradignac A, Simon C, Burrus-Mehl F, Schlienger JL, Singer L. Eating behavior and depression before and after antidepressant treatment: a prospective, naturalistic study. J Affect Disord. 1994;30(3):193–207.
98. Lloyd GG, Lishman WA. Effect of depression on the speed of recall of pleasant and unpleasant experiences. Psychol Med. 1975;5:173–80.
99. Nelson RE, Craighead WE. Selective recall of positive and negative feedback, self-control behaviors, and depression. J Abnorm Psychol. 1977;86:379–88.
100. Lewinsohn PM, Youngren MA, Grosscup SJ. Reinforcement and depression. In: Depue A, editor. The psychobiology of depressive disorders: implications for the effects of stress. New York: Academic; 1979.

101. Alloy L, Abramsom L. Judgement of contingency in depressed and nondepressed students: sadder but wiser? J Exp Psychol Gen. 1979;108:441–85.
102. Beck A. Cognitive theory of depression. New York: Wiley; 1979.
103. Strauss GP, Frank MJ, Waltz JA, Kazanova Z, Herbener ES, Gold JM. Deficits in positive reinforcement learning and uncertainty-driven exploration are associated with distinct aspects of negative symptoms in schizophrenia. Biol Psychiatry. 2011;69(5):424–31.
104. Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. Psychol Med. 1996;26(3):591–603.
105. Elliott R, Sahakian BJ, Michael A, Paykel ES, Dolan RJ. Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression. Psychol Med. 1998;28:559–71.
106. Shah PJ, O'Carroll RE, Rogers A, Moffoot AP, Ebmeier KP. Abnormal response to negative feedback in depression. Psychol Med. 1999;29:63–72.
107. Steffens DC, Wagner HR, Levy RM, Horn KA, Krishnan KR. Performance feedback deficit in geriatric depression. Biol Psychiatry. 2001;50(5):358–63.
108. Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. Brain. 2007;130(Pt 9):2367–74.
109. Marco-Pallares J, Cucurell D, Cunillera T, Kramer UM, Camara E, Nager W, Bauer P, Schule R, Schols L, Munte TF, Rodriguez-Fornells A. Genetic variability in the dopamine system (dopamine receptor D4, catechol-O-methyltransferase) modulates neurophysiological responses to gains and losses. Biol Psychiatry. 2009;66(2):154–61.
110. Marco-Pallares J, Cucurell D, Cunillera T, Garcia R, Andres-Pueyo A, Munte TF, Rodriguez-Fornells A. Human oscillatory activity associated to reward processing in a gambling task. Neuropsychologia. 2008;46(1):241–8.
111. Padrao G, Mallorqui A, Cucurell D, Marco-Pallares J, Rodriguez-Fornells A. Neurophysiological differences in reward processing in anhedonics. Cogn Affect Behav Neurosci. 2013;13(1):102–15.
112. Gehring WJ, Willoughby AR. The medial frontal cortex and the rapid processing of monetary gains and losses. Science. 2002;295(5563):2279–82.
113. Miltner W, Braun C, Coles M. Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a generic neural system for error detection. J Cogn Neurosci. 1997;9:788–98.
114. Muller S, Moller J, Rodriguez-Fornells A, Munte T. Brain potentials related to self-generated and external information used for performance monitoring. Clin Neurophysiol. 2005;116:63–74.
115. Cohen MX. Error-related medial frontal theta activity predicts cingulate-related structural connectivity. Neuroimage. 2011;55(3):1373–83.
116. Walsh MM, Anderson JR. Learning from experience: event-related potential correlates of reward processing, neural adaptation, and behavioral choice. Neurosci Biobehav Rev. 2012;36(8):1870–84.
117. Luque D, Lopez FJ, Marco-Pallares J, Camara E, Rodriguez-Fornells A. Feedback-related brain potential activity complies with basic assumptions of associative learning theory. J Cogn Neurosci. 2012;24(4):794–808.
118. Schultz W. Behavioral dopamine signals. Trends Neurosci. 2007;30(5):203–10.
119. Nieuwenhuis S, Yeung N, Holroyd C, Schurger A, Cohen J. Sensitivity of electrophysiological activity from medial frontal cortex to utilitarian and performance feedback. Cereb Cortex. 2004;14(7):741–7.
120. Cavanagh JF, Frank MJ, Klein TJ, Allen JJB. Frontal theta links prediction errors to behavioral adaption in reinforcement learning. Neuroimage. 2010;49:3198–209.
121. Marco-Pallares J, Camara E, Munte TF, Rodriguez-Fornells A. Neural mechanisms underlying adaptive actions after slips. J Cogn Neurosci. 2008;20(9):1595–610.
122. Trujillo LT, Allen JJ. Theta EEG dynamics of the error-related negativity. Clin Neurophysiol. 2007;118:645–68.
123. Cavanagh JF, Figueroa CM, Cohen MX, Frank MJ. Frontal theta reflects uncertainty and unexpectedness during exploration and exploitation. Cereb Cortex. 2012;22(11):2575–86.

124. Cunillera T, Fuentemilla L, Periañez J, Marco-Pallares J, Kramer UM, Camara E, Munte TF, Rodriguez-Fornells A. Brain oscillatory activity associated with task switching and feedback processing. Cogn Affect Behav Neurosci. 2012;12(1):16–33.
125. Tzur G, Berger A. Fast and slow brain rhythms in rule/expectation violation tasks: focusing on evaluation processes by excluding motor action. Behav Brain Res. 2009;198(2):420–8.
126. van de Vijver I, Ridderinkhof KR, Cohen MX. Frontal oscillatory dynamics predict feedback learning and action adjustments. J Cogn Neurosci. 2011;23(12):4106–21.
127. Womelsdorf T, Johnston K, Vinck M, Everling S. Theta-activity in anterior cingulate cortex predicts task rules and their adjustments following errors. Proc Natl Acad Sci U S A. 2010;107(11):5248–53.
128. Luu P, Tucker DM, Makeig D. Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. Clin Neurophysiol. 2004;115(8): 1821–35.
129. Cohen MX, Elger CE, Ranganath C. Reward expectation modulates feedback-related negativity and EEG spectra. Neuroimage. 2007;35(2):968–78.
130. HajiHosseini A, Rodriguez-Fornells A, Marco-Pallares J. The role of beta-gamma oscillations on unexpected reward processing. Neuroimage. 2012;60:1678–85.
131. Hallschmid M, Molle M, Fisher S, Born J. EEG synchronization upon reward in man. Clin Neurophysiol. 2002;113(1059):1065.
132. Courtemanche R, Fuji N, Graybiel AM. Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. J Neurosci. 2003;23:11741–52.
133. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J Abnorm Psychol. 2012;121(3):553–8.
134. Berenbaum H, Snowhite R, Oltmanns TF. Anhedonia and emotional responses to affect evoking stimuli. Psychol Med. 1987;17(3):677–84.
135. Germans MK, Kring AM. Hedonic deficit in anhedonia: support for the role of approach motivation. Pers Individ Differ. 2000;28:659–72.
136. Foti D, Hajcak G. Depression and reduced sensitivity to non-rewards versus rewards: evidence from event-related potentials. Biol Psychol. 2009;81(1):1–8.
137. Santesso DL, Steele KT, Bogdan R, Holmes AJ, Deveney CM, Meites TM, Pizzagalli DA. Enhanced negative feedback responses in remitted depression. NeuroReport. 2008;19(10): 1045–8.
138. Tucker DM, Luu P, Frishkoff G, Quiring J, Poulsen C. Frontolimbic response to negative feedback in clinical depression. J Abnorm Psychol. 2003;112(4):667–78.
139. Matsumoto M, Matsumoto K, Abe H, Tanaka K. Medial prefrontal cell activity signaling prediction errors of action values. Nat Neurosci. 2007;10:647–56.
140. Oliveira FT, McDonald JJ, Goodman D. Performance monitoring in the anterior cingulate is not all error related: expectancy deviation and the representation of action-outcome associations. J Cogn Neurosci. 2007;19:1994–2004.
141. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. J Pers Soc Psychol. 1994;67(2):319–33.
142. Torrubia R, Ávila C, Molto J, Caseras X. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers Individ Differ. 2001;31:837–62.
143. Pizzagalli DA, Losifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. J Psychiatr Res. 2008;43(1):76–87.
144. Simons RF, MacMillan III FW, Ireland FB. Anticipatory pleasure deficit in subjects reporting physical anhedonia: slow cortical evidence. Biol Psychol. 1982;14(3–4):298–310.
145. Klein D. Depression and anhedonia. In: Clark DC, Fawcett J, Clark DC, Fawcett J, editors. Anhedonia and affect deficit states. New York: PMA; 1984. p. 1–14.

146. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. PLoS One. 2009;4(8):e6598.
147. Miller GA. Information processing deficits in anhedonia and perceptual aberration: a psychophysiological analysis. Biol Psychiatry. 1986;21(1):100–15.
148. Giese-Davis JE, Miller GA, Knight RA. Memory template comparison processes in anhedonia and dysthymia. Psychophysiology. 1993;30(6):646–56.
149. Yee CM, Miller GA. A dual-task analysis of resource allocation in dysthymia and anhedonia. J Abnorm Psychol. 1994;103(4):625–36.
150. Dubal S, Pierson A, Jouvent R. Focused attention in anhedonia: a P3 study. Psychophysiology. 2000;37(5):711–4.
151. Hazlett EA, Dawson ME, Filion DL, Schell AM, Nuechterlein KH. Autonomic orienting and the allocation of processing resources in schizophrenia patients and putatively at-risk individuals. J Abnorm Psychol. 1997;106(2):171–81.
152. Simons RF, Russo KR. Event-related potentials and continuous performance in subjects with physical anhedonia or perceptual aberrations. J Psychophysiol. 1987;2:27–37.
153. Strayer DL, Kramer AF. Attentional requirements of automatic and controlled processing. J Exp Psychol Learn Mem Cogn. 1990;16:67–82.
154. Franken IH, Van Strien JW, Nijs IM. Effect of hedonic tone on event-related potential measures of cognitive processing. Psychiatry Res. 2006;142(2–3):233–9.
155. Josiassen RC, Shagass C, Roemer RA, Straumanis JJ. Attention-related effects on somatosensory evoked potentials in college students at high risk for psychopathology. J Abnorm Psychol. 1985;94(4):507–18.
156. Ward PB, Catts SV, Armstrong MS, McConaghy N. P300 and psychiatric vulnerability in university students. Ann N Y Acad Sci. 1984;425:645–52.
157. Yee CM, Deldin PJ, Miller GA. Early stimulus processing in dysthymia and anhedonia. J Abnorm Psychol. 1992;101(2):230–3.
158. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 2002;3(3):201–15.
159. Bruder GE, Tenke CE, Towey JP, Leite P, Fong R, Stewart JE, McGrath PJ, Quitkin FM. Brain ERPs of depressed patients to complex tones in an oddball task: relation of reduced P3 asymmetry to physical anhedonia. Psychophysiology. 1998;35(1):54–63.
160. Brunia CH, Hackley SA, van Boxtel GJ, Kotani Y, Ohgami Y. Waiting to perceive: reward or punishment? Clin Neurophysiol. 2011;122(5):858–68.
161. Fuentemilla L, Cucurell D, Marco-Pallares J, Guitart-Masip M, Moris J, Rodriguez-Fornells A. Electrophysiological correlates of anticipating improbable but desired events. Neuroimage. 2013;78:135–44.
162. Moris J, Luque D, Rodriguez-Fornells A. Learning-induced modulations of the stimulus-preceding negativity. Psychophysiology. 2013;50(9):931–9.

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