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Neural signatures of saliency-mapping in anhedonia: A narrative review

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Abstract

Anhedonia is the loss of pleasure or motivation to engage in previously enjoyable activities, and is a transdiagnostic symptom associated with significant clinical impairment. Anhedonia is implicated in several different psychiatric disorders, presenting a promising opportunity for transdiagnostic treatment. Thus, developing targeted treatments for anhedonia is of critical importance for population mental health. An important first step in doing so is establishing a thorough understanding of the neural correlates of anhedonia. The Triple Network Model of Psychopathology provides a frame for how brain activity may go awry in anhedonia, specifically in the context of Salience Network (SN) function (i.e., saliency-mapping). We present a narrative review examining saliency-mapping as it relates to anhedonia severity in depressed and transdiagnostic adult samples. Results revealed increased anhedonia to be associated with hyperactivity of the SN at rest and in the context of negative stimuli, as well as a global lack of SN engagement in the context of positive stimuli. Potential treatments for anhedonia are placed within this model, and future directions for research are discussed.

Keywords

Salience network; Anhedonia; Reward processing

1. Introduction

Anhedonia—the loss of pleasure or motivation to engage in potentially enjoyable activities—is a clinical symptom associated with significant impairment in the context of several different psychiatric disorders. In depression, anhedonia is associated with poorer response to treatments (Downar et al., 2014; McMakin et al., 2012; Vrieze et al., 2013), and a more chronic course of illness (Spijker et al., 2001). Anhedonia in substance use disorders is

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Conflict of interest

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associated with lower rates of abstinence during treatment, as well as increased odds of relapse in studies of smoking cessation (Crits-Christoph et al., 2018; Leventhal et al., 2014). Prospectively, anhedonia may be a key explanatory mechanism for how individuals with anxiety disorders may go on to develop depression (Winer et al., 2017). Further emphasizing its clinical importance, anhedonia is strongly associated with suicidal ideation, regardless of depression diagnosis (Ducasse et al., 2018). Given both its transdiagnostic nature as well as its significant clinical impact, developing targeted treatments for anhedonia is of the utmost importance.

One key barrier to developing transdiagnostic treatments for anhedonia is that it has historically been overlooked as a primary focus of treatment or research. This oversight is largely due to anhedonia's current classification as a *symptom* of several different disorders, rather than a *disorder* itself (American Psychiatric Association, 2013). For this reason, extant research on anhedonia has largely been conducted in the context other disorders (e.g., depression, schizophrenia), for which anhedonia is not required for diagnosis.

A clear example of this limitation is in neuroimaging research. Anhedonia is thought to represent the behavioral and emotional consequences of a hypoactive reward system in the brain (Der-Avakian and Markou, 2012), making it a neurobiologically informed symptom which falls squarely within RDoC's positive valence domain criteria (Insel et al., 2010). In spite of this conceptualization, the majority of studies examining reward-related dysfunction do so in the context of broader diagnostic categories (e.g., depression), rather than transdiagnostically. Thus, while reward-related dysfunction in depression has been well characterized (for a comprehensive review, see Ng et al., 2019), how reward-related deficits specifically relate to anhedonia is largely unknown.

In an effort to facilitate a comprehensive neuroscientific understanding of this impairing clinical symptom, the present review consolidates findings on neural correlates specific to anhedonia, both within the diagnostic category of depression and in individuals not selected based on a clinical diagnosis. Taking a translational approach, this review highlights these findings in terms of a larger conceptual model (e. g., Triple Network Model of Psychopathology), in order to increase the dissemination of these findings across disciplines (e.g., clinical psychology, cognitive neuroscience). Overall, this review is intended to serve two critical purposes: (1) to present a current understanding of neural activation and connectivity associated with anhedonia, and (2) to relay these findings in a manner that will bring clinical psychology and neuroscience communities together in order to jumpstart neurobiologically-informed treatment research.

We lay the foundation for this review with a description of the principal theoretical framework under which these findings will be interpreted (i.e., the Triple Network Model of Psychopathology). Having outlined the neural and cognitive details of this model, we then begin the review with an examination of the relationship between neural correlates of saliency-mapping and hedonic function in psychopathology free (PF) samples. From there, we discuss how this system functions when hedonic capacity is clinically impaired, in the context of anhedonia. Although anhedonia is considered a core symptom of both depression and schizophrenia, recent work suggests that there may be differences at the level of reward

processing (Lambert et al., 2018) and treatment response (Bodén et al., 2021) in the context of these two disorders. For this reason, we have limited the scope of this narrative review to anhedonia in the context of individuals with depression or without a psychiatric diagnosis. Consistent with our aims of mapping clinical symptomatology onto brain behavior, only peer-reviewed studies which directly assessed anhedonia through self-report, and tested how individual differences in these symptoms mapped onto brain activity, are included in this review. We conclude with a discussion of how studies examining treatments for anhedonia can contribute to our understanding of saliency-mapping, and how this understanding has direct implications for future research on a broad range of clinical syndromes.

1.1. Triple Network Model of Psychopathology

The functional organization of the brain, as measured by the correlation in timeseries of distributed cortical regions, is of growing empirical and clinical interest. Functional connectivity analyses have offered novel insights into the macroscale networks underlying complex cognitive processes, and demonstrated a consistent core of functional networks. Three of these intrinsically connected networks dynamically interact to orchestrate goal-directed behaviors: the Default Mode Network (DMN), the Central Executive Network (CEN), and the Salience Network (SN; Chen et al., 2013; Dosenbach et al., 2007; Fox et al., 2005). These networks are reliably identified across both task-based and resting state fMRI analyses (Power et al., 2011; Shehzad et al., 2009). While the DMN facilitates cognition that is independent of immediate perceptual input or directed thought, and shows greater activity during periods of rest, engagement of the CEN is critical for external, goal-directed processes (Koechlin and Summerfield, 2007; Miller and Cohen, 2001; Müller and Knight, 2006; Petrides, 2005). In contrast, the SN is responsible for detecting salient stimuli in the environment, and allocating cognitive resources to facilitate goal-directed behavior (Menon & Uddin, 2010). The DMN and the CEN are often found to be functionally anticorrelated (Whitfield-Gabrieli and Ford, 2012), such that decreases in DMN activation facilitate cognitive shifts that improve performance on external goal-oriented tasks. Thus, the more suppressed the DMN is, the better performance is (Weissman et al., 2006; Whitfield-Gabrieli and Ford, 2012). Though it is possible to characterize these networks as relatively independent and consistent systems, interactions between networks help to modulate higher-order processes, and dependencies between these networks are therefore critical to psychopathology. As proposed in the Triple Network Model of Psychopathology (Figure 1), the SN mediates this critical relationship between the CEN and DMN (Menon & Uddin, 2010). Positioned within the SN are key regions implicated in emotion, sensory, interoceptive, and reward processing (e.g., amygdala, nucleus accumbens [NAcc], ventral tegmental area [VTA], thalamus; Menon & Uddin, 2010). From these subcortical regions, the insulae receive a stream of information from which salient stimuli are identified in a bottom-up fashion (Menon & Uddin, 2010). Increased connectivity and activation within the SN is associated with reward processing functions including anticipation and response of positive stimuli (Keller et al., 2013; Zou et al., 2018).

Within the SN, the insulae communicate this information to the dACC, which has direct outputs to the motor cortices to facilitate action selection (Menon, 2015). Outside of the SN, the insulae communicate with both the CEN and DMN, to engage the CEN, and disengage

the DMN in the presence of salient stimuli (Menon & Uddin, 2010). The engagement of the SN is therefore a critical first step to executing goal-directed behaviors. As an illustration, more efficient stopping during a stop signal task is associated with increased activation in the SN, coupled with decreased activation of the DMN (Ray Li, 2006; Sharp et al., 2010). Moreover, deficits in connectivity within the SN (i.e., between the insula and dACC) are associated with a failure to deactivate the DMN (Bonnelle et al., 2012), and poorer performance (Li et al., 2019) during cognitive tasks.

The Triple Network Model of Psychopathology posits that psychopathology may develop through inefficient saliency-mapping by the SN (Menon, 2011). Saliency-mapping refers to the process through which the SN detects salient stimuli in one's environment and communicates with the CEN and DMN to allocate cognitive resources (Menon, 2011). Though reward processing is an aspect of SN function (e.g., identification of potentially and actually rewarding stimuli; updating of reward value of a stimulus), it is the saliency-mapping function of the SN that supports effective reward-based learning and behavior through engagement of the CEN and disengagement of DMN in the presence of a salient stimuli. This model has been applied to several different disorders, with results supporting the hypothesis that deficits in saliency-mapping can contribute to clinical impairment. For example, individuals with anxiety disorders have consistently shown hyperactivity of the insula and amygdala (regions located in the SN) in response to negatively-valenced stimuli, and this exaggerated saliency-mapping process is hypothesized to contribute to downstream avoidance behaviors (Paulus and Stein, 2006). Individuals with autism spectrum disorders, in contrast, exhibit hypoactivity of the insula (i.e., decreased saliency-processing) in response to social cues, which may contribute to difficulties engaging in social situations and interpreting social cues (Di Martino et al., 2009). Given the relationship between anhedonia and reward circuitry, it is likely that deficits in saliency-mapping play a role in contributing to the significant clinical impairment seen in anhedonia. Examination of inter- and intra-connectivity of the SN as a whole, including but also extending beyond traditional reward circuity, has the potential to provide a more mechanistic understanding of alterations of brain activity that may contribute to anhedonia. As such, the present review will use the Triple Network Model of Psychopathology to examine how saliency-mapping mediated by the SN is related to anhedonia.

2. Saliency-Mapping

2.1. Saliency-mapping in individuals without psychopathology

Regardless of stimulus valence, greater hedonic capacity (i.e., a dispositional ability to experience pleasure in response to stimuli that are typically rewarding) maps onto increased activation of the SN in psychopathology free (PF) samples. Specifically, activation of the SN (insula, NAcc, OFC, caudate) during the anticipation of (Ubl et al., 2015; Zou et al., 2018), as well as in response to (Keller et al., 2013; Wacker et al., 2009; Zou et al., 2018) salient stimuli increases as a function of hedonic capacity in PF adults. Studies have also shown that this increase in SN activation during saliency-mapping is often coupled with decreases in activation of the DMN (right vmPFC, right middle temporal gyrus) during processing of salient stimuli (Harvey et al., 2007; Wacker et al., 2009). This finding not only supports the

role of the DMN in task-negative thought, but also supports the idea that the SN modulates cognition when hedonic rewards are present. In line with this view, in order to facilitate sustained attention to and engagement with salient stimuli, greater hedonic capacity in PF individuals is also associated with increased connectivity within the SN (NAcc and VTA with superior temporal gyrus, insula, and left OFC; Keller et al. 2013).

In addition to studies probing time-locked responses to salient stimuli, some studies have looked at how hedonic capacity maps onto reward-learning neural signals. A reward prediction error (RPE) signal, indicating the difference between the expected outcome and the actual outcome, is the driving force behind reward learning (McClure et al., 2003). Critical to the integration of this RPE into behavioral change, is the release of dopamine which signals 'incentive salience' (Berridge and Robinson, 1998; Pessiglione et al., 2006). As reward learning takes place, there is an expected temporal transition of brain activity from the RPE signal upon receipt of reward, to a reward expectancy (RE) signal during the anticipation of a reward. In PF individuals, there is a strong inverse relationship between RPE and RE signals in the SN (VS) as learning takes place (Greenberg et al., 2015). Indeed, underlining the importance of the RPE for motivation, PF individuals show a significant association between RPE and self-reported anticipation, but not consumption, of reward (Cooper et al., 2014).

Overall, individuals without anhedonia tend to show increased saliency-mapping in response to salient stimuli. Specifically, these findings paint a picture of saliency-mapping in PF individuals wherein greater levels of hedonic capacity are associated with (1) increased activation of SN regions, (2) deactivation of DMN regions, and (3) increased intra-SN connectivity to identify and sustain engagement.

2.2. Saliency-mapping in clinical populations

With an understanding of how individual differences in hedonic capacity relate to saliency-mapping in PF populations, we will now shift to an exploration of how this process may go awry in clinical populations. As indicated previously, although anhedonia is implicated in several different psychiatric disorders, the scope of this review is limited to depressed, and transdiagnostic samples.

We begin by first examining resting-state dynamics in the SN, in the absence of any salient stimuli. Notably, in clinical samples, the lower individual hedonic capacity (i.e., greater anhedonia), the more activated their SN appears to be at baseline or rest. This hyperactivity is largely driven by increased activity of the NAcc, a region largely associated with processing motivation and reward (Ikemoto and Panksepp, 1999). Specifically, lower hedonic capacity is associated with increased connectivity between the SN (NAcc) and CEN (dmPFC), as well as connectivity within the DMN and CEN (Gong et al. 2018; Sharma et al. 2017). Nonetheless, parsing the SN is far from clear. Findings regarding intra-SN connectivity are mixed, with the most consistent findings relating to connectivity with the NAcc. Specifically, lower levels of hedonic capacity are associated with increased NAcc connectivity with some regions of the SN (insula, mOFC; Park et al., 2017; Sharma et al., 2017), but decreased connectivity between other SN regions (caudate, mOFC, insula, VTA; Gong et al. 2018; Park et al. 2017). Critically, heightened activity of the NAcc at rest is

consistent with what is seen in PF samples during saliency-mapping and may suggest that hedonic capacity in clinical populations may be driven by erroneous signaling in the NAcc.

Findings regarding connectivity between the SN and DMN are also mixed. While one study conducted in a transdiagnostic clinical sample found a negative association between anhedonia and connectivity between the SN and the DMN (Sharma et al., 2017), another study conducted in a depressed sample found a positive association (NAcc, putamen to vmPFC; Felger et al., 2016). Moreover, a third study conducted in a depressed sample failed to find any relationship between anhedonia and connectivity between the SN (NAcc, VTA) and DMN (pvmPFC; Young et al., 2016). These discrepant findings may be, in part, explained by findings from a study conducted by Yang and colleagues (2017). In their study comparing PF controls to depressed participants, the depressed group showed a unique relationship between anhedonia and connectivity between the SN and DMN (Yang et al., 2017). Specifically, while anticipatory anhedonia was positively associated with connectivity between the SN (caudate) and the DMN (middle temporal gyri), consummatory anhedonia was negatively associated with connectivity between the SN (caudate) and another region of the DMN (cuneus; Yang et al., 2017). As shown in Table 1, Yang and colleagues were the only ones to collect measures of both anticipatory and consummatory anhedonia, therefore it remains unclear if their findings may explain the discrepancy. That being said, this suggests that different facets of anhedonia (e.g., anticipatory, consummatory) may be uniquely related to the level of connectivity between the SN and DMN at rest.

While in PF individuals increased SN activity during saliency-mapping of rewarding stimuli is reliably associated with greater hedonic experience, clinical populations show a more complicated pattern when faced with rewarding stimuli. While some contexts evoke a similar pattern wherein SN activation varies as a function of hedonic capacity, others do not. On the one hand, activity in regions of the SN (caudate, insula, putamen, amygdala) while passively viewing personally relevant rewarding images (Keedwell et al., 2005), and during reward anticipation (Duprat et al., 2017) show a positive association with hedonic capacity in clinical samples. On the other hand, in other contexts, hedonic capacity has failed to show any relation to activation in several of the same regions of the SN. For example, activation in the caudate, putamen, NAcc, and amygdala in response to passive viewing of emotional pictures and faces (Connolly et al., 2015; Stuhrmann et al., 2013), and reward outcome (Pizzagalli et al., 2009) show no association with hedonic capacity.

Notably, there is one region of the SN that shows a slightly different relationship with hedonic capacity, depending on the context. During the anticipation of reward, the OFC shows a similar pattern wherein greater hedonic capacity maps onto greater activation (Ubl et al., 2015). However, while viewing rewarding images, the OFC shows the opposite association: greater activation corresponding with lower hedonic capacity (Keedwell et al., 2005). In addition to the OFC during reward consumption, several regions of the DMN (vmPFC, PCC, precuneus, rACC) and the CEN (inferior frontal gyrus; Jenkins et al., 2018; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005) show greater response to positive stimuli as hedonic capacity decreases. Lower hedonic capacity is also positively associated with connectivity between the CEN (dmPFC) and the DMN (PCC; Zhang et al. 2017), but negatively associated with connectivity between the DMN (pvmPFC) and the SN (NAcc,

VTA, SN; Young et al. 2016). The interaction of these networks may suggest that the SN is failing to act as a "switch" to downregulate the DMN and upregulate the CEN in the context of positively salient stimuli.

In a study examining how the relationship between RPE and RE signals relates to hedonic capacity symptoms in a collapsed sample of PF and individuals with depression, lower hedonic capacity was associated with a smaller inverse relationship between RPE and PE in the right VS, and this association remained true after controlling for depressive symptom severity (Greenberg et al., 2015). In a study of depressed adults, lower levels of hedonic capacity were associated with blunted RPE signals in the VS and the mOFC, and this association remained significant after controlling for depressive symptoms (Rothkirch et al., 2017). These findings broadly suggest that anhedonia is associated with an impaired ability to integrate reward information and predict future rewards in the VS.

Negative stimuli evoke a different pattern of SN activation in clinical populations: a global increase in activity. Lower hedonic capacity is associated with increased activation in specific regions of the SN (amygdala, insula; Kumar et al., 2017), as well as increased connectivity between regions in the SN (VS, caudate, MCC; Quevedo et al., 2017), thus lending support for both the hyperactivity and the hyper-connectivity theories of anhedonia. In addition to this increase in SN activity and connectivity, lower hedonic capacity is also associated with an increase in activity within one region of the CEN (vlPFC; Kumar et al., 2017).

Findings in another region of the SN, the habenula, have been mixed in response to negative stimuli. One study found a positive association between response to monetary loss in this region and anhedonia (Liu et al., 2017), while another failed to find any association (Lawson et al., 2017). Although both studies examined habenula response to monetary loss in depressed samples, there is one key difference which may account for these discrepant findings: which self-report questionnaires were utilized. Both studies did not find a significant association between habenula response and anhedonia, when measured using the Snaith Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), but the study conducted by Liu and colleagues found a significant relationship using a second anhedonia measure; the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006). This potentially speaks to key differences in different facets of anhedonia that these scales are measuring, and the importance of establishing a universal measure of anhedonia.

This hypersensitivity to negative stimuli, coupled with the lack of saliency-mapping in response to positive stimuli paints a very specific picture of how hedonic capacity may come into play in saliency-mapping. As increased bias toward negative stimuli is commonly a symptom that is thought to characterize depression rather than anhedonia, it is important to note that only the studies conducted by Liu and Lawson controlled for depressive symptoms, while the others did not. Given the significant overlap between anhedonia and depression, it will be critical for future work to replicate findings regarding hypersensitivity to negative stimuli in anhedonia while controlling for depression severity. Moreover, further research is still needed to see if there are any additional contributions of hypersensitivity to negative stimuli to anhedonia specifically. For example, it is possible that hypersensitivity to negative

stimuli limits reward-based learning by differentially activating CEN to negative versus positive stimuli. Another possibility highlights the potential importance of the habenula in this process. When considering the role of the habenula relative to the other SN regions implicated in processing of negative stimuli (e.g., amygdala, insula), the habenula is uniquely associated with the inhibition of dopamine signaling in response to unexpected negative outcomes (Hikosaka et al., 2008). It is possible that higher levels of habenula activation are responsible for inhibiting reward-related dopaminergic responses.

Overall, these findings support a picture of inefficient saliency-mapping in anhedonia which is characterized by: (1) hyperactivity of the SN at rest, (2) lack of engagement of SN in response to positive stimuli, (3) hyperactivation of the SN in response to negative stimuli. These patterns of saliency-mapping are in stark contrast to the patterns seen in PF individuals, who demonstrate increased engagement of the SN in the context of rewarding stimuli. Thus, these results suggest that anhedonia is specifically related to an inability to activate the SN in response to positively-salient stimuli, and aberrant intra- and inter-SN connectivity in response to all types of salient stimuli.

3. Translational lessons from treatment

There are three broad classes of interventions that have been shown to have varying levels of effectiveness in anhedonia: psychotherapeutic, pharmacologic, and neuromodulatory. What follows is an overview of findings related to anhedonia in these three areas, in the service of further elucidating the neural correlates of saliency-mapping. Critically, all studies reviewed in this section were conducted with depressive symptoms as the primary treatment target. As such, although all studies included collected self-report measures of anhedonia, the findings specific to anhedonia are sparse. When available, findings related to depression are presented.

3.1. Psychotherapy

Behavioral Activation Therapy for Depression (BATD) has been a key focus of anhedonia psychotherapy-based research, owing to its proposed mechanism of action: increasing engagement with rewarding activities in daily life (Lejuez et al., 2011). BATD therapists work collaboratively with patients to come up with activities that are likely to be meaningful and rewarding, and then work hierarchically to increase the patient's participation in these activities. Two key studies conducted by Smoski, Dichter and colleagues have tested the impact of BATD on anhedonia in depressed adults. The first of the two studies did not find a significant decrease in self-reported anhedonia; however, the authors did report three noteworthy changes as a result of treatment: (1) a significant decrease in depressive symptoms, coupled with (2) increased activation during the anticipation of reward in regions of the SN (caudate, insula), and the CEN (left cingulate gyrus, left frontal gyrus) and (3) decreased activation during the receipt of rewards in the SN (right caudate, left paracingulate gyrus; Dichter et al., 2009). Given that this pattern of increased SN activity during the anticipation of positive stimuli was hypothesized to predict improvements in anhedonia, it is surprising that this was not the case. It is also somewhat unexpected that decreased activation in the SN during the receipt of rewards was associated with amelioration of

depressive symptoms. These findings await replication, and may be a function of the small sample size (n=16 in the depressed group).

In a second study with a larger sample size, this group did find a significant decrease in anhedonia (as well as depressive symptoms) as a result of BATD treatment (Carl et al., 2016). Moreover, higher levels of anhedonia at baseline were predictive of a greater reduction in depressive symptoms over the course of treatment (Carl et al., 2016). Several neurosignatures at baseline predicted reduction in anhedonia. First, during instructed upregulation of positive emotion, decreased connectivity within the CEN (left middle frontal gyrus, right tempoparietal junction) was associated with greater declines in anhedonia over the course of treatment (Walsh et al., 2019). Second, during the anticipation of rewards, greater decreases in connectivity between certain regions of the SN (left putamen,subcallosal cortex) between runs of the reward task, coupled with greater overall connectivity between other regions of the SN (left caudate, right paracingulate gyrus) were associated with a greater decrease in anhedonia (Walsh et al., 2017). Broadly these findings suggest that individuals who are less able to sustain saliency-mapping processes (e.g., through ongoing activation of the SN, or through engagement of the CEN during instructed upregulation of emotion) may benefit the most from BATD.

3.2. Pharmacologic interventions

A recent systematic review examining 17 studies that directly measured the impact of psychotropic medications on anhedonia found that several different classes of medications (e.g., monoaminergic, glutamatergic, psychedelic, and stimulant) showed efficacy, albeit at varying levels (Cao et al., 2019). Only three studies, however, examined the neural correlates of these anti-anhedonic effects.

In a trial of open-label ketamine, augmented with either placebo or riluzole, ketamine infusions led to a rapid reduction in anhedonia, with no added benefit from riluzole (Lally et al., 2015). Positron emission tomography (PET) scans showed that a reduction in anhedonia was significantly associated with an increase in metabolism in one region of the SN (dACC), and a decrease in another region of the SN (OFC) while controlling for depressive symptoms (Lally et al., 2015).

Another study administered small (2 mg) doses of nicotine to depressed non-smokers (Janes et al., 2018). Although nicotine did not significantly reduce anhedonia in this sample, level of anhedonia did influence the effect the nicotine had on participants at the level of brain activity. Specifically, those with high anhedonia showed the greatest increase in connectivity between the SN (NAcc) and DMN (rACC) at rest as a result of nicotine administration. However, as this change did not result in a significant reduction in anhedonia, conclusions cannot be drawn regarding the relationship between these neural signatures and symptom improvement.

In a randomized controlled trial comparing venlafaxine and fluoxetine, individuals with depression showed a significant reduction in anhedonia over the course of treatment, with no significant effect of drug type (Light et al., 2011). At baseline, a smaller change in CEN (right vlPFC) activity when shifting from maintenance to suppression of positive

emotion was associated with greater reduction in anhedonia over the first 8 weeks of treatment (Light et al., 2011). Importantly, this finding was unique to positive affect, as there was no relationship between activation in the right vlPFC and the suppression and/or maintenance of negative affect. This finding suggests that venlafaxine and fluoxetine may be most effective for individuals who show less modulation of the CEN when actively modulating responses to positive stimuli. Under-modulation of CEN in reward contexts may reflect ineffective saliency-mapping by the SN, and identification of pharmacological agents that impact saliency mapping functions may be an important step in optimizing treatments for anhedonia.

In one of the only studies examining treatment in a transdiagnostic anhedonic sample, Krystal and colleagues showed that 8 weeks of treatment with a selective kappa-opioid receptor antagonist significantly reduced anhedonia in a sample of adults with anhedonia and a mood and/or anxiety disorder (2020). Moreover, this treatment resulted in a significant increase in SN (VS) activation during the anticipation of reward. It is unclear if increased VS activation during anticipation of reward was associated with other network changes, such as more efficient modulation of CEN and DMN. Future research may address inter- and intra-network modulation as a mechanism of successful treatment.

3.3. Neuromodulation

3.3.1. Deep brain stimulation—Deep Brain Stimulation (DBS) is an invasive neuromodulatory technique that involves placing a high frequency stimulating electrode on a specific region on the brain. To the author's knowledge, two studies to date have tested DBS of the SN, specifically targeting the NAcc, while measuring anhedonia in the context of treatment resistant depression. The first study (n=3), did not find statistically significant indicators of decreased anhedonia via self-report questionnaires, although the authors did note that the participants anecdotally reported an increase in motivation to seek out previously enjoyable activities (Schlaepfer et al., 2008). This study also found that one week of DBS increased metabolism in regions of the SN (NAcc, amygdala) and the CEN (dlPFC, dmPFC) and decreased metabolism in one region of the DMN (vmPFC), as well as one region of the CEN (vlPFC; Schlaepfer et al., 2008). A second study conducted by the same group with a slightly larger sample size (n=10) did find a significant anti-anhedonic effect for all participants after one month, and even more so for treatment responders (as defined by a decreased in depressive symptoms) at 12 months (Bewernick et al., 2010), and this effect was maintained at 24 months (Bewernick et al., 2012). This study showed slightly different findings in terms of metabolic impact: increased metabolism in the amygdala was seen in responders only, with sample-wide decreases in one region of the DMN (SCG) and one region of the SN (OFC; Bewernick et al., 2010). Although the findings are mixed with regards to the CEN, these studies do support a pattern of increased metabolism in the SN, and decreased metabolism in the DMN corresponding with symptom improvement in anhedonia as a result of DBS to the NAcc.

Two studies examining DBS of another region that falls within the SN (medial forebrain bundle) report notable improvements in appetitive motivation in participants (Fenoy et al., 2016; Schlaepfer et al., 2013), however they did not collect anhedonia measures and

therefore it cannot be determined if this clinical increase in motivation translated to an improvement in anhedonia symptoms.

In a novel approach to target identification, Scangos and colleagues utilized multi-site electrodes to systematically measure symptom response based on DBS target (2021). In their case study, they found that DBS of the SN (VS) produced the most consistent benefit for a middle-aged woman with treatment resistant depression whose core symptom was anhedonia (Scangos et al., 2021).

Taken together, these results suggest that DBS of the SN may improve anhedonia by increasing saliency-mapping capabilities (e.g., increase SN and CEN metabolism to identify and engage with salient stimulus while decreasing metabolism in the DMN).

3.3.2. Transcranial magnetic stimulation—Two different types of Transcranial Magnetic Stimulation (TMS) have been used to treat anhedonia: high-frequency stimulation of regions of the CEN, and low-frequency stimulation of the SN. These treatment regiments have advanced on the idea that high-frequency (> 5 Hz) pulses result in local excitation of the underlying cortex, while low-frequency (< 5 Hz) pulses induce inhibition (however, see Bestmann, 2008 for an alternative view on the neural consequences of stimulation frequency). In a study conducted by Downar and colleagues, higher levels of anhedonia at baseline were associated with poorer response to 10 Hz rTMS of the dmPFC (as measured by decrease in depressive symptoms; 2014). Another study found a bi-modal distribution of responses to intermittent Theta Burst Stimulation (iTBS) – a faster type of neuromodulation, similar in method to high-frequency rTMS – of the dlPFC based on severity of anhedonia (Duprat et al., 2017). While at baseline, individuals with low anhedonia showed increased activation in SN regions (caudate, putamen) in response to reward when compared to those with high anhedonia, this pattern was differentially modulated as a result of iTBS. One week of iTBS resulted in increased activity in SN regions (caudate, putamen) within the high-anhedonia group, but a decrease in activity in these same regions within the low-anhedonia group (Duprat et al., 2017). Unfortunately, this change in SN activation did not correspond to significant changes in anhedonia, so these results should be interpreted with caution. However, these findings do suggest that iTBS of a CEN region can lead to downstream changes in the SN.

Only two studies have directly shown promising results by using rTMS to treat anhedonia. The first is a pilot study which augmented the effects of neuromodulation with a psychotherapeutic intervention, by training rTMS staff to administer brief Behavioral Activation (BA) therapy to participants in the 5–10 minutes prior to each administration of rTMS (Russo et al., 2018). This intervention resulted in significant improvement in anhedonia in 39% (n=4) of the total sample. Although Russo and colleagues note that the rTMS utilized in their study targeted the left prefrontal cortex, they do not indicate a specific region that was the target nor do they indicate the frequency utilized. Interestingly, another study showed a signal change in anhedonia utilizing an entirely different approach and target region: low-frequency (i.e., inhibitory) rTMS of the SN (right OFC; Fettes et al., 2017). In this case study, Fettes and colleagues show that rTMS of the OFC resulted in significant

improvement in anhedonia for an individual with treatment refractory depression who failed to respond to rTMS of the dlPFC and dmPFC (Fettes et al., 2017).

A recent randomized sham-controlled trial utilized transcranial direct current stimulation (tDCS) – another non-invasive neuromodulatory technique that aims to increased cerebral blood flow to target regions – targeting the left dlPFC (Jog et al., 2021). This study found a significant improvement in anhedonia in the active relative to control condition, and noted that a greater tDCS-induced BOLD-signal change near the left dlPFC at baseline was associated with a greater decrease in anhedonia over the course of treatment (Jog et al., 2021). Of note, the authors did not find any association between change in anhedonia and current-induced magnetic fields or simulated current densities in the left dlPFC, which suggests that BOLD-signal change in response to tDCS at baseline may be uniquely qualified to be a biomarker of treatment response in anhedonia.

Another study assessed anhedonia in response to rTMS of the dlPFC at two levels of analysis: behaviorally, using a novel “Happy Faces” task which asked participants to indicate whether any positive affect is shown on a human face, and subjectively using self-report (Light et al., 2019). This study showed a significant reduction in anhedonia via behavioral task performance (i.e., improvement in correct identification of subtle expressions of happiness) over the course of treatment, and that this varied as a function of anhedonia self-report scores after controlling for depressive symptoms (Light et al., 2019). Thus, while neuromodulation-based therapies for anhedonia offer promise, the parameter space is still largely unexplored, and the field has yet to develop a rigorous targeting or treatment approach specific to anhedonic symptomatology.

4. Discussion

This review is the first to synthesize findings specifically related to saliency-mapping in anhedonia. Articles reviewed for this paper were limited to those which measured anhedonia directly through self-report, and related these symptoms to fMRI-based findings. Moreover, although anhedonia is a transdiagnostic symptom, studies which examined anhedonia in the context of disorders other than depression were outside of the scope of this review.

We offer here consistent support for impaired saliency-mapping in anhedonia in accordance with the Triple Network Model for Psychopathology. In PF individuals, increased hedonic experience is associated with increased SN activity, intra-SN connectivity, and decreased activity in the DMN while processing salient stimuli. In contrast, clinical levels of anhedonia are associated with relative hyperactivity of the SN at rest, which is also seen in the context of negative stimuli, and a global lack of engagement of the SN in the context of rewarding stimuli. In further support of this association between aberrant saliency-mapping and anhedonia, treatments that have shown the most success at reducing anhedonia directly target the SN (VS, OFC). Although results from this review support a pattern of saliency-mapping deficits in anhedonia, much more specificity should be gleaned from future studies. We identify three critical limitations in the current literature preventing a fuller understanding of anhedonia’s neural representation.

First, in terms of measuring anhedonia, a key barrier to synthesizing the current findings is the lack of a universal measure of anhedonia. As a clinical symptom, anhedonia is best assessed using patient self-report or clinician rating. However, there is not a standard scale used across studies. As shown in Table 1, across the 47 studies included in this review, anhedonia was assessed in 16 different ways. By far, the most commonly used scale was the SHAPS (Snaith et al., 1995a), but even this scale was only used in 44% of the studies. Importantly, there are several different ways to score the SHAPS, and although most studies report the mean scores within their samples, not all report how the SHAPS was scored, making it impossible to compare anhedonia severity across samples. Given that significant differences in anhedonia severity may account for some of the conflicting findings, this is a critical barrier which must be addressed in future work. The second most commonly cited scale in this review was the anhedonic subscale of the Mood and Symptom Questionnaire (MASQ; Watson et al., 1995). As the name implies, this subscale of the MASQ was developed specifically to capture low positive affect in the context of depression, rather than anhedonia on its own. In fact, this particular subscale has been shown to function independently as a depression-screening tool (Bredemeier et al., 2010). The use of items from depression scales to capture anhedonia is not uncommon. Several studies in this review also used subscales from the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), the Inventory of Depressive Symptomatology (IDS; Rush et al., 1996), the Hamilton Depression Rating Scale (HAMD; Hamilton, 1967), the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) among others. Methodologically these scales measure anhedonia as it presents in depression, rather than independently, and it is likely that the usage of these subscales is a consequence of anhedonia being involved in exploratory or secondary analysis, rather than original study design. Future work must focus on developing a gold standard measure for anhedonia which can be used across studies.

A second limitation is that the current review was fundamentally limited in scope by the dependence on depressive cohorts, and therefore excluded anhedonia in the context of disorders other than depression; this is largely representative of the state of the field. Consistent with the NIMH's Research Domain Criteria (RDoC; Insel et al., 2010) initiative, anhedonia is a transdiagnostic symptom. Anhedonia is captured within the RDoC domain of Positive Valence Systems, which indexes how individuals process and interact with rewarding stimuli in their environment. Future work should study anhedonia in transdiagnostic samples in order to gain generalizable knowledge that will facilitate transdiagnostic treatment development. Also consistent with the RDoC approach, it will be critical to assess how function in different RDoC Systems may interact (e.g., between Cognitive and Positive Valence Systems), which could have the potential to explain why reward function deficits may also differ between diagnostic groups (e.g., depression and schizophrenia). Given that the results from this review suggest that anhedonia may be the result of dysfunctional activation of saliency-mapping processes at rest, and a consequent lack of appropriate engagement of these regions in the context of salient stimuli, future neuroimaging studies should focus on dynamic tasks wherein reward state is changing, and in which the global patterns of dynamic change can be assessed within the Triple Network Model framework. Graph theoretical approaches offer a clear opportunity to directly assess how more global network dynamics shift from rest to reward-state in anhedonia. Critically,

graph theory techniques often offer convenient summary statistics describing how distributed network dynamics change (e.g., segregation, integration, topographical organization) may influence the relationship between saliency-mapping and anhedonia. The potential of this technique in anhedonia research has not yet been realized; while a robust characterization of the network deficits associated with anhedonia has yet to be reported, the value of such applications extends beyond mere description and may in fact be used in a diagnostic capacity, and even model the progression of the neural correlates of psychopathy after adjuvant therapies.

In spite of its transdiagnostic nature, anhedonia has typically been studied in the context of other psychiatric disorders rather than as a disorder itself. Given its clinical significance and ubiquity, anhedonia presents a promising transdiagnostic treatment target. This review utilized the Triple Network Model of Psychopathology to assess the possible neural dependencies of anhedonia, and how saliency-mapping deficits may influence anhedonia-driven behaviors. Results from this review suggest that, relative to PF individuals, those with clinically significant levels of anhedonia do show deficits in how they process and integrate information about salient stimuli. While largely convergent on the notion that anhedonia is associated with deficits in saliency-mapping, this analysis nonetheless suggests that a standard measure of anhedonia must be established and consistently utilized in order to allow for comparison across studies. Finally, a more developed neuroimaging assessment, including task-based reinforcement learning paradigms, and a graph theoretical approach to parse regions within the SN and CEN should be utilized in future studies to gain specificity regarding state-based network dynamics in anhedonia.

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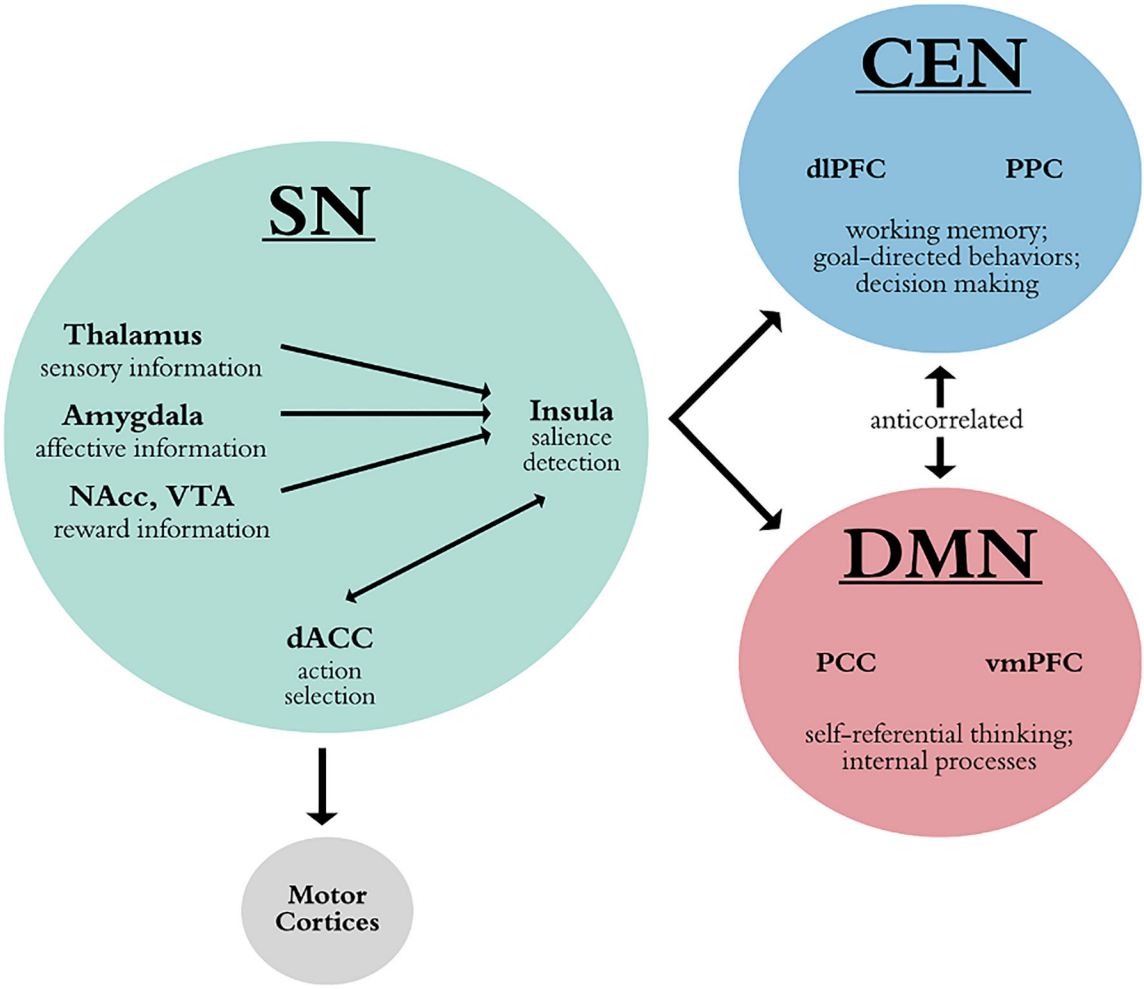

Fig. 1.

Schematic diagram of saliency-mapping in the Triple Network Model of Psychopathology. Adapted from Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 214, 655–667. https://doi.org/10.1007/s00429-010-0262-0

Table 1

Studies included in the present review (in order of appearance in text)

Study	*N* (M/F)	Diagnosis	Anhedonia Scale Used
Ubl et al., 2015	28 (13, 15)	HC	SHAPS
Zou et al., 2018	25 (12, 13)	HC	CPAS; CSAS; TEPS
Keller et al., 2013	21 (9, 12)	HC	MASQ-Anhedonic depression subscale
Wacker et al., 2009	28 (14, 14)	HC	MASQ-Anhedonic depression subscale
Harvey et al., 2007	29 (14, 15)	HC	CPAS
Greenberg et al., 2015	31 (12, 19)	HC	SHAPS, MASQ-Anhedonic depression subscale
Cooper et al., 2014	38 (20, 18)	HC	TEPS, SHAPS, BDI-II subscale[a]
Gong et al., 2018	68 (33, 42)	MDD	TEPS
Sharma et al., 2017	225 (110, 115)	transdiagnostic	BAS-Reward sensitivity subscale
Park et al., 2017	22 MDD (7, 12)	MDD	SANS Avolition–Apathy and Anhedonia–Associality subscale sum
Felger et al., 2016	48 (14, 34)	MDD + BD (all in current MDE)	SHAPS; IDS-SR subscale[b]
Young et al., 2016	21 (10, 11)	MDD	MASQ-Anhedonia depression subscale
Yang et al., 2017	40 (21, 19)	MDD	SHAPS, TEPS
Keedwell et al., 2005	12 (4, 8)	MDD	FCPS
Duprat et al., 2017	37 (10, 27)	MDD	SHAPS
Connolly et al., 2015	51 (all female)	MDD	IDS-C subscale[c]
Stuhrmann et al., 2013	35 (14, 21)	MDD	CSAS, CPAS
Pizzagalli et al., 2009	30 (15, 15)	MDD	BDI-II subscale[a]
Ubl et al., 2015	30 (14, 16)	MDD	SHAPS
Jenkins et al., 2018	12 (all male)	MDD	SHAPS
Zhang et al., 2017	21 (8, 13)	MDD	SHAPS
Greenberg et al., 2015	109 (38, 71)	MDD + HC (findings across all participants)	SHAPS; MASQ-Anhedonic depression subscale
Rothkirch et al., 2017	28 (13, 15)	MDD	SHAPS
Kumar et al., 2017	34 (15, 19)	MDD + HC (findings across all participants)	SHAPS
Quevedo et al., 2017	68 (24, 44)	MDD + HC (findings across all participants)	SCI-MOODS subscale[d]
Liu et al., 2017	21 (9, 12)	MDD	SHAPS; TEPS
Lawson et al., 2017	25 (15, 10)	MDD	SHAPS
Dichter et al., 2009	12 (6, 6)	MDD	JAM; BAS
Carl et al., 2016	33 (11, 22)	MDD	BDI-II subscale[a]
Walsh et al., 2019	33 (11, 22)	MDD	BDI-II subscale[a]
Walsh et al., 2017	33 (11, 22)	MDD	BDI-II subscale[a]
Lally et al., 2015	52 (33, 19)	MDD	SHAPS
Janes et al., 2018	18 (10, 8)	MDD	SHAPS
Light et al., 2011	27 (12, 15)	MDD	MASQ – Anhedonic depression subscale
Krystal et al., 2020	89 (33, 56)	anhedonia + mood or anxiety disorder	SHAPS

Study	*N* (M/F)	Diagnosis	Anhedonia Scale Used
Schlaepfer et al., 2008	3 (2, 1)	MDD	Composite score (items from MADRS and HAMD)[e]
Bewernick et al., 2010	10 (6, 4)	MDD	HLPA
Bewernick et al., 2012	11 (7,4)	MDD	HLPA
Fenoy et al., 2016	4 (2,2)	MDD	subjective report from patient and clinician
Schlaepfer et al., 2013	7 (4,3)	MDD	subjective report from patient and clinician
Scangos et al., 2021	1 (female)	MDD	subjective report from patient and clinician
Downar et al., 2014	47 (20, 27)	MDD + BD (all in current MDE)	Composite score (items from BDI-II, QIDS)[f]
Duprat et al., 2017	37 (10, 27)	MDD	SHAPS
Russo et al., 2018	11 (all female)	MDD	SHAPS
Fettes et al., 2017	1 (female)	MDD	IDS-C subscale[g]
Jog et al., 2021	59 (27, 32)	MDD	SHAPS
Light et al., 2019	19 (7, 12)	MDD	SHAPS

[a] unofficial BDI-II subscale consists of items 4 ("*satisfaction with things*"), 12 ("*interest in other people*"), 15 ("*effort in doing things*"), and 21 ("*interest in sex*")

[b] unofficial IDS-SR subscale consists of items 9 ("*response of mood to good or desired events*"), 19 ("*general interest*") and 21 ("*capacity for pleasure or enjoyment*").

[c] unofficial IDS-C subscale consists of items 19 ("*interest/involvement*") and 21 ("*capacity for pleasure*").

[d] unofficial SCI-MOODS subscale consists of items assessing "lack of interest across a number of areas of behavior such as friends, romantic relationships and previously enjoyed activities as well as loss of fun and pleasure."

[e] unofficial composite score consists of the following items from MADRS: "*apparent sadness*," "*concentration difficulties*," *lassitude*," "*inability to feel*", and the following from HAMD: "*work and activities"* and "*genital symptoms*."

[f] unofficial composite score consists of items #2 and #4 from BDI-II, item #13 on QIDS.

[g] unofficial subscale consists of item 21 "*pleasure/enjoyment from activities*." BAS = Behavioral Activation Scale (Carver and White, 1994), BDI-II = Beck Depression Inventory-II (Beck et al., 1996), CPAS = Chapman Scale for Physical Anhedonia (Chapman et al., 1976), CSAS = Chapman Scale for Social Anhedonia (Chapman et al., 1976), FCPS = Fawcett-Clark Pleasure Capacity Scale (Fawcett et al., 1983), HAMD = Hamilton Depression Rating Scale (Hamilton, 1967), HLPA = Hautzinger's list of positive activities (Hautzinger, 2000; Lewinsohn and Graf, 1973), IDS-C/SR = The Inventory of Depressive Symptomatology – Clinician-Rated/Self-Rated (Rush et al., 1996), Jackson Appetitive Motivation Scale (Jackson and Smillie, 2004), MADRS = Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg, 1979), MASQ = Mood and Symptom Questionnaire (Watson et al., 1995), QIDS = Quick Inventory of Depressive Symptomatology (Rush et al., 2003), SANS = Scale for the Assessment of Negative Symptoms (Andreasen, 1984), SCI-MOODS = Structured Clinical Interview for Mood Spectrum (Fagiolini et al., 1999), SHAPS = Snaith Hamilton Pleasure Scale (Snaith et al., 1995), TEPS = Temporal Experience of Pleasure Scale (Gard et al., 2006).