

Evaluating State-Based Network Dynamics in Anhedonia

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy
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ABSTRACT

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Abstract

Anhedonia refers to the loss of motivation to engage in previously enjoyable activities. While anhedonia is most often characterized as a symptom of psychiatric disorders such as depression, schizophrenia, and posttraumatic stress disorder, it can also present on its own. In spite of this, it is typically overlooked as a primary focus of research studies due to limitations inherent to our current diagnostic system. Therefore, no targeted treatments for anhedonia exist despite the significant impairment it causes. Moreover, very few studies to date have explored underlying neuropsychological characteristics of anhedonia, which is essential to the development of effective treatments for this clinical target. Because anhedonia is a core clinical target spanning many disorders as well as existing as its own disorder, transdiagnostic treatment approaches are of critical scientific importance to improve population mental health.

The present study addresses this gap in the literature by taking a graph theoretical approach to characterizing state-based (i.e., reward anticipation, rest) network dynamics in a transdiagnostic sample of adults with clinically significant anhedonia ($n = 77$). Analyses focused on three canonical brain networks: the Salience Network (SN), the Default Mode Network (DMN) and the Central Executive Network (CEN). Owing to the direct inputs from reward-related regions to the SN, hypotheses centered on anhedonia relating to deficits in connectivity within the SN, as well as between the SN and the other networks.

Two models were tested. First, a multiple linear regression assessed to what extent connectivity within the SN, as well as between the SN and the other two networks

(i.e., CEN, DMN) during reward anticipation related to anhedonia. To build on these findings and assess dynamic state changes as they relate to anhedonia, a second multiple linear regression explored whether the magnitude of topographical reorganization that took place within the SN as well as between the SN and the other two networks predicted anhedonic severity in this sample. Contrary to hypotheses, neither connectivity within the SN or between the SN and the CEN or DMN during reward anticipation, nor reorganization within the SN or between the SN and the CEN or DMN when transitioning from rest to reward anticipation were associated with anhedonia severity in this sample.

Exploratory analyses looked beyond the SN and found a significant association between anhedonia severity and DMN reorganization between rest and reward anticipation. Specifically, greater anhedonia severity was associated with less reorganization in response to reward anticipation. This finding suggests that anhedonia may be associated with DMN hyposensitivity, such that individuals with more severe anhedonia may have a difficult time disengaging from their internal world in the context of potentially rewarding experiences. Very little is known about the internal experience of anhedonia, and future work should focus on examining what internal thought processes these individuals may be having difficulty disengaging from. Nonetheless, an impaired ability to attend to the external world when potential reinforcers are present can prevent individuals from coming into contact with rewarding experiences in their environments and be a key maintaining factor of anhedonia.

Although preliminary, these findings challenge the centrality of the SN in anhedonia and suggests the importance of the DMN. Future studies should aim to replicate this finding and explore potential clinical implications. Specifically, treatments that foster the ability to flexibility redirect attention to the present moment, such as mindfulness-based cognitive therapies, or non-invasive neuromodulatory therapies that target the DMN, may be particularly promising interventions for anhedonia.

Dedication

To the patients who have given me the privilege of being their therapist. Thank you for trusting me and for teaching me.

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1. Introduction*

Anhedonia—the loss of pleasure or motivation to engage in potentially enjoyable activities—is associated with significant impairment in the context of several different psychiatric disorders. In depression, anhedonia is associated with a poorer response to treatment (Downar et al., 2014; Khazanov et al., 2020; 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 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 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). Critically, although anhedonia frequently presents in the context of other clinical diagnoses, it can also present at clinically impairing levels on its own (see study sample in Cernasov et al., 2021a). Given both its transdiagnostic nature as well as its significant clinical impact, developing targeted treatments for anhedonia is of the utmost importance.

* A portion of this section is based on the following publication: Pisoni, A., Davis, S. W., & Smoski, M. (2021). Neural signatures of saliency-mapping in anhedonia: A narrative review. *Psychiatry Research*, 304, 114123.

1.1 Barriers to Treatment Development

There are two key barriers that stand in the way of developing transdiagnostic treatments for anhedonia: (1) the way anhedonia is currently classified, and (2) the lack of a network-level characterization of anhedonia.

1.1.1 Classification of Anhedonia

Despite evidence that anhedonia can present independently of other diagnoses, it has historically been overlooked as a primary focus of treatment and 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 actually required for diagnosis.

A clear example of this limitation is in neuroimaging research. One predominant viewpoint is that anhedonia is thought to represent one of the behavioral and emotional consequences of a hypoactive reward system in the brain (Der-Avakian & Markou, 2012), which has propelled research in this area in hopes of identifying potential treatment targets. However, the majority of the studies examining reward-related dysfunction in anhedonia have done so in the context of broader diagnostic categories (e.g., depression), rather than focusing transdiagnostically on anhedonia. Thus, while reward-related dysfunction in depression, for example, has been well characterized (for a

comprehensive review, see Ng et al., 2019), how reward-related deficits specifically relate to anhedonia is largely unknown.

Further highlighting the limitations of conceptualizing anhedonia as a symptom rather than a disorder, very little is known about the subjective experience of anhedonia. Although there is a bounty of research characterizing the internal experience of disorders such as depression, posttraumatic stress disorder, and schizophrenia, for which anhedonia is a common but not required symptom for diagnosis, any repetitive thinking patterns, action urges, or general affective experience unique to anhedonia remain unknown. The subjective or internal experience of a psychological disorder is particularly important for treatment development and is nearly impossible to glean without research studies examining a specific symptom or disorder (i.e., anhedonia) independently.

1.1.2 Examination of Neural Correlates of Anhedonia

A second barrier to treatment development is the lack of a true circuit-level characterization of anhedonia. Most findings relating anhedonia to brain activity have been univariate in nature, focusing on how extracted timeseries from specific regions of interest relate to other variables of interest (i.e., clinical symptoms). These univariate findings have been largely inconsistent. For example, while some studies have found a significant association between reward-related activation in the ventral striatum (VS) and anhedonia in the context of depression (Der-Avakian & Markou, 2012; Misaki et al., 2016), others have failed to find any association (Arrondo et al., 2015; Connolly et al., 2015; Foti et al., 2014; Jenkins et al., 2018; Mies et al., 2013; Pizzagalli et al., 2009; Stuhmann et al., 2013). A similar pattern of inconsistency exists when examining

anhedonia in the context of schizophrenia as well as posttraumatic stress disorder, wherein some studies have found an association between VS activation and anhedonia (Arrondo et al., 2015; Dowd & Barch, 2010; Pessin et al., 2021), while others have not (Mehta et al., 2020; Simon et al., 2010).

These conflicting findings may be at least partly attributable to the fact that univariate analyses only capture a portion of the complex brain system. Recent evidence suggests that clinical impairment is the result of large-scale dysfunctional connectivity between canonical neural networks (Menon, 2011; Whitfield-Gabrieli & Ford, 2012). Thus, the functional network organization of the brain, as measured by the correlation in timeseries of distributed cortical regions, is of growing empirical and clinical interest. Characterizing anhedonia using neural network dynamics may offer superior explanatory value compared to the traditionally utilized univariate analyses of activity in isolated brain regions.

1.2 Addressing Barriers

With these barriers in mind, an intuitive next step is to assess network dynamics of anhedonia in a transdiagnostic clinical sample. Two specific frameworks, the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) initiative (Insel et al., 2010), as well as the Triple Network Model of Psychopathology (Menon, 2011), provide ideal conceptualizations with which to address these barriers.

1.2.1 Research Domain Criteria

In 2009, the NIMH proposed a new research framework, RDoC, offering a novel method of classifying psychopathology dimensionally (Insel et al., 2010).

Acknowledging the heterogeneity inherent in the current clinical diagnostic system (i.e., two individuals diagnosed with depression could have completely different symptom profiles), RDoC categorized psychopathology into six broad domains. Anhedonia can be conceptualized as an independent disorder within this model, and is likely captured within the Positive Valence Systems domain, which indexes how individuals attend to, process, and interact with rewarding stimuli in their environment. Utilizing the RDoC framework to classify anhedonia as its own clinical construct, independent of other diagnoses, allows for a thorough exploration of what is specific to anhedonia versus a consequence of the larger diagnostic categories.

1.2.2 Triple Network Model of Psychopathology

The Triple Network Model of Psychopathology, similarly, allows for a more complex and nuanced exploration of anhedonia. The model leverages novel insights from functional connectivity analyses suggesting the existence of macroscale networks underlying complex cognitive processes. Specifically, the Triple Network Model of Psychopathology (Figure 1), posits that psychopathology can develop when connectivity goes awry either within or between three specific canonical brain networks (Menon, 2011).

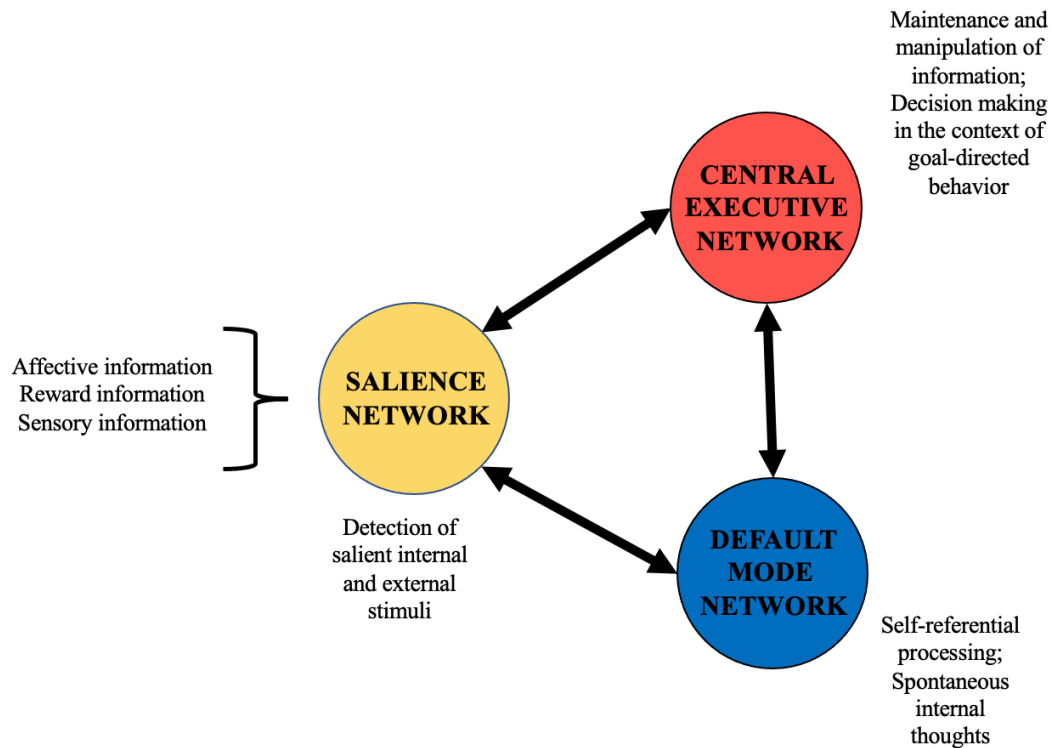


Figure 1: Triple Network Model of Psychopathology

Note. Figure adapted from (Menon, 2011). Left bracket indicates input streams into the Salience Network.

1.2.2.1 The Three Networks

The model comprises the Default Mode Network (DMN), the Central Executive Network (CEN), and the Salience Network (SN; Menon, 2011). These networks have been reliably identified across both task based and resting state fMRI studies (Power et al., 2011; Shehzad et al., 2009) and dynamically interact to orchestrate goal-directed behaviors, as described below.

As illustrated in Figure 1, the SN receives input from key regions implicated in affective, sensory, and reward processing (e.g., amygdala, nucleus accumbens [NAcc], ventral tegmental area [VTA], thalamus; Menon & Uddin, 2010). From these subcortical regions, the SN receives a stream of information from which salient stimuli are identified in a bottom-up fashion (Menon & Uddin, 2010). When a salient stimulus is present, the SN communicates with the other two networks to draw attention to the salient stimulus.

While the DMN facilitates internally oriented cognition (e.g., self-referential processing, spontaneous internal thoughts), and shows greater activity during periods of rest, engagement of the CEN is critical for external, goal-directed processes through its maintenance and manipulation of information and facilitation of decision making (Koechlin & Summerfield, 2007; Miller & Cohen, 2001; Müller & Knight, 2006; Petrides, 2005). In this way, the DMN and the CEN are often found to be functionally anticorrelated (Whitfield-Gabrieli & Ford, 2012), and their relationship can mark the shift from an individual's focus on their internal world (i.e., DMN dominance) to their external world and potential external goals (i.e., CEN dominance). Thus, in the presence of an external salient stimulus, the SN will attempt to engage the CEN, and disengage the DMN (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 are associated with a failure to deactivate the DMN (Bonnelle et al., 2012), and poorer performance (L. M. Li et al., 2019) during cognitive tasks.

1.2.2.2 Saliency-Mapping

Saliency-mapping refers to the specific process through which the SN detects salient stimuli in one's environment and communicates with the CEN and DMN to allocate cognitive resources to allow for interaction with and/or attainment of the salient stimulus (Menon, 2011). Though reward processing contributes to 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 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 & Stein, 2006). Individuals with autism spectrum disorders, in contrast, exhibit hypoactivity of the insula (i.e., decreased saliency-mapping) 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 proposed relationship between anhedonia and reward circuitry, it is possible that deficits in saliency-mapping play a role in the significant clinical impairment seen in anhedonia. This is supported by a recent narrative review assessing studies that directly related anhedonic severity with activation and connectivity of the SN and found evidence of deficits in saliency-mapping in this population (Pisoni et

al., 2021). However, as noted in Section 1.1.1, the majority of studies that have contributed to the characterization of anhedonia as being related to reward-circuitry deficits – including those included in the aforementioned review article – have been conducted in depressed samples. Therefore, the role of saliency-mapping in anhedonia remains an empirical question.

1.3 The Present Study

Leveraging these models (RDoC, Triple Network Model), the present study utilizes novel techniques rooted in graph theory to assess network dynamics in a transdiagnostic clinical sample of adults with anhedonia. Specifically, the study probes saliency-mapping in the context of two different affective states: rest and anticipation of reward.

First, network-based connectivity during the anticipation of potential rewards, and the extent to which this relates to anhedonia severity was assessed. Owing to the theoretical support of saliency-mapping deficits playing a role in anhedonia, it was hypothesized that greater anhedonia severity would be associated with less connectivity within the SN, as well as between the SN and the DMN, and between the SN and the CEN. This was assessed utilizing two indices of functional connectivity characterizing how these three canonical networks interact during the activation of the reward network (e.g., anticipation of reward): within-network connectivity and between-network connectivity.

To build on these findings, how these networks dynamically change in organization when transitioning from rest to reward-state was also assessed. Because the

SN plays a critical role in overall network dynamics (i.e., shifting between CEN and DMN dominance), a presumptive downstream effect of deficits in saliency-mapping is a lack of overall network shift in response to rewards. It was therefore hypothesized that greater anhedonia severity would be associated with decreased reward-related reorganization within the SN, as well as between the SN and the other two networks (i.e., CEN and DMN).

2. Methods

2.1 Recruitment and Procedures

Data used in the present study was from a NIMH-funded multi-site clinical trial (FAST-MAS; Contract #: HHSN271201200006I; PI: Andrew Krystal, MD). The primary aims of the parent study were to test the efficacy of a κ Opioid Receptor (KOR) antagonist in treating anhedonia in a transdiagnostic sample. The study utilized advanced neuroimaging techniques and self-report measures administered at several time-points (i.e., before, during, and after treatment) to assess the impact of treatment. The current study utilizes baseline (i.e., pre-treatment) neural and self-report measures from all study participants (see Figure 2).

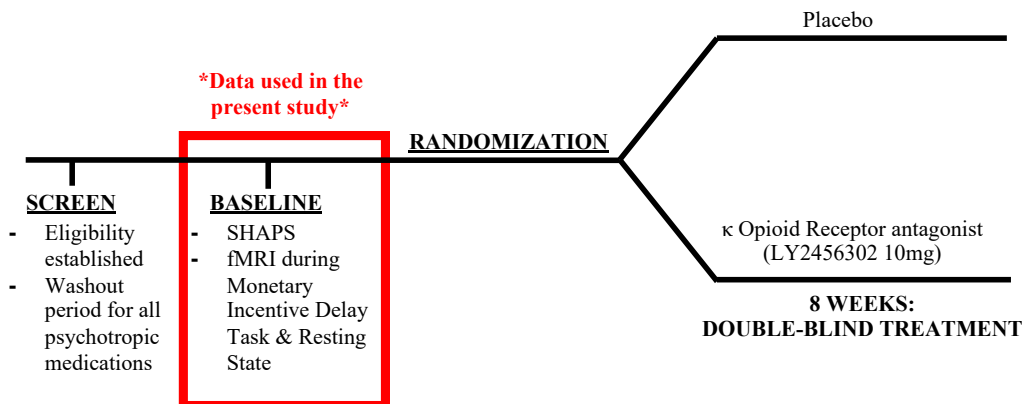


Figure 2: Overview of Parent Study

Participants were recruited via clinical referral, advertisement, and through other outreach efforts at each of six study sites (Yale University, Mt. Sinai School of Medicine, Baylor College of Medicine, Case Western Reserve University, Indiana University, and Duke University). Given the multisite nature of the study, study personnel were stringent in their standardization, with consistent monitoring of assessment and study protocols across sites (see Krystal et al., 2018 for details). The final study sample included 89 adults ages 21-65, with an average of 14 participants enrolled at each site. At baseline all participants were assessed using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to establish clinical diagnosis in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994), as participants were required to meet criteria for one of the following: major depressive disorder, bipolar I or II (in a current depressed state), generalized anxiety disorder, social phobia, panic disorder, or posttraumatic stress disorder.

In addition to meeting DSM-IV diagnostic criteria for one of these disorders, all participants were required to have clinically elevated levels of anhedonia. This was defined as a score of greater than or equal to 20 on the Snaith Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS is a well-validated 14-item self-report questionnaire that assesses hedonic capacity. The SHAPS total score is derived by summing the responses to each item, with higher scores corresponding to higher levels of anhedonia. ROC analyses suggest that a SHAPS score of ≥ 20 corresponds to clinically significant anhedonia from a general population sample (Krystal et al., 2020).

Once eligibility was established, participants completed a baseline visit within 30 days of their intake. Data included in the present study are exclusively from this baseline visit, during which the SHAPS was collected again at the same time as the fMRI scan.

2.2 Participants

Of the 89 participants with data from the parent study, two were excluded due to fMRI task malfunction, and 10 were excluded due to excessive motion (greater than 0.3mm framewise displacement) across more than 2 task blocks, resulting in a final sample of 77 participants (48 women, age range = 21 – 65 years, $M = 37.81$, $SD = 12.69$). The final sample had mean anhedonia scores consistent with what has been seen in other clinical samples ($M = 35.03$, $SD = 7.64$; Trøstheim et al., 2020). For a full breakdown of the primary DSM-IV diagnoses of all participants in the final sample, see Table 1. The final sample was predominantly (68.8%) white. Additionally, 18.2% of participants identified as Black or African American, 3.9% as Asian, 1.3% as American Indian or Alaska Native, and 7.8% as holding more than one racial identity. Eight percent of the final sample identified as Hispanic or Latinx. There were no differences between included and excluded participants in terms of anhedonia severity. There was a statistically significant difference in age, such that participants who were excluded from the analyses were on average 11.8 years younger than those included, $t(87) = -3.046$, $p = 0.003$. Fishers exact test was used to compare the distributions of race and ethnicity across included versus excluded participants. There were no differences between groups in terms of distribution of ethnicity ($p = 0.619$). Regarding race, there were not significant differences of distribution of participants identifying as Black or African

American, Asian, American Indian or Alaska Native, or as holding more than one racial identity (all p s $>.05$). However, there was a significant difference between groups for those who did not disclose their racial identity ($p = 0.017$). Specifically, all individuals ($n = 2$) who endorsed “unknown” as their racial identity were in the excluded group.

Table 1: Primary Clinical Diagnoses of Final Sample

DSM-IV Diagnosis	<i>n</i>	%
Bipolar I Disorder, Current	2	2.6
Bipolar I Disorder, Past	2	2.6
Bipolar II Disorder, Current	3	3.9
Bipolar II Disorder, Past	2	2.6
Generalized Anxiety Disorder, Current	14	18.2
Major Depressive Disorder, Current	26	33.8
Major Depressive Disorder, Recurrent	18	23.4
Panic Disorder, Current	3	3.9
Posttraumatic Stress Disorder, Current	2	2.6
Social Anxiety Disorder, Generalized	4	5.2
Social Anxiety Disorder, Non-Generalized	1	1.3

Note. Primary clinical diagnoses of all included participants, as assessed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998).

2.3 fMRI Acquisition

MRI data were collected on 3.0 Tesla MRI scanners (5 Siemens, 1 General Electric) running the latest software version using an advanced 32-channel RF coil. The MRI session started with a localizer scan. Following, the functional images were acquired using the following specifications: TR/TE = 2000/30ms, flip angle = 70 deg, FOV = 25.6 cm, matrix = 64x64, 32 axial slices, acceleration factor = 2, voxel size = 4x4x4 mm, 137

fMRI time points + 4 dummy scans at the beginning (total 141 points/TRs), with a total scan time of 4 min 42 seconds (141 x 2 s) for each run. The functional images were collected over five runs. Next, a single run of resting-state images was collected under the same specifications as noted during the task. Diffusion-weighted images were also collected but are not reported here. Finally, a high-resolution anatomical image (128 axial slices to cover whole brain, voxel size = 1x1x1 mm) was collected. An MR compatible video projection system with vision correction lenses, headphones and a button box were used for fMRI task presentation and response capture.

2.4 Functional MRI Data Processing

Figure 3 provides an overview of the processing pipeline.

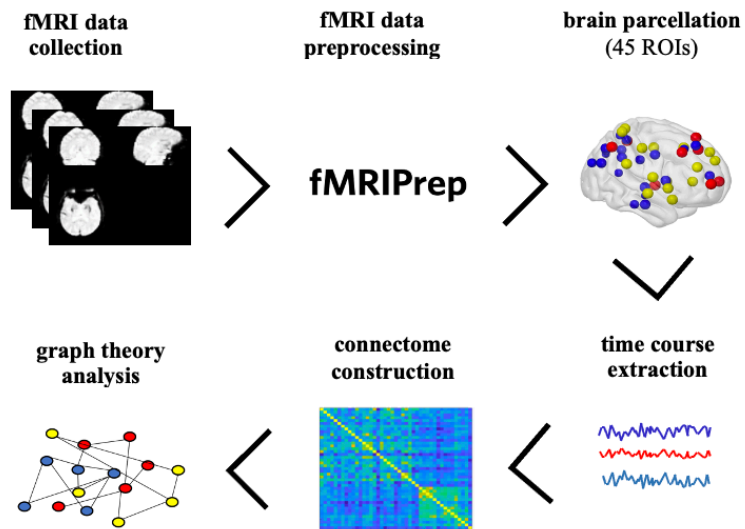


Figure 3: Overview of Processing Pipeline

2.4.1 Preprocessing*

Quotations in this section denote automatically generated text from *fMRIPrep* based on preprocessing steps utilized. The creators of *fMRIPrep* request that this text, which is released under the CC0 license, be used verbatim in manuscripts in order to increase reproducibility and transparency.

For each run, the first four functional images were discarded to allow for scanner equilibrium. Preprocessing was performed using *fMRIPrep* 20.2.3 (Esteban et al., 2019, 2022; RRID:SCR_016216), which is based on *Nipype* 1.6.1 (Esteban et al., 2021; Gorgolewski et al., 2011; RRID:SCR_002502).

2.4.1.1 fMRIPrep

The decision to use *fMRIPrep* for preprocessing was made for several important reasons. Preprocessing fMRI data is meant to ensure researchers extract a signal that is an accurate representation of actual neural activity. However, there are significant inconsistencies in the specific preprocessing pipelines and tools different research groups use, which contributes to a lack of reproducibility (Andronache et al., 2013). To maximize the clinical benefit of rapidly advancing neuroimaging technologies, it is critical to prioritize reliability and reproducibility.

fMRIPrep addresses these concerns as a standardized, open-source, preprocessing pipeline (Esteban et al., 2019). *fMRIPrep*'s workflow leverages a combination of tools

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from common fMRI preprocessing packages, utilizes a modular design to allow for both anatomical and functional pipelines, and maximizes transparency and ease of quality control by producing thorough and easy to interpret visual reports. Moreover, in order to use *fMRIPrep*, researchers must first format their data into Brain Imaging Data Structure (BIDS; K. J. Gorgolewski et al., 2016). BIDS maximizes the potential benefit of neuroimaging data by providing a standardized method of storing and organizing neuroimaging and behavioral data. Utilizing the BIDS format also makes the fMRI data computer-readable, which ensures the reusability and shareability of raw data.

2.4.1.2 Anatomical Data Preprocessing

“A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.3.3 (Avants et al., 2008; RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL 5.0.9, RRID:SCR_002823, Y. Zhang et al., 2001). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial

normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* (Fonov et al., 2009; RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym).”

2.4.1.3 Functional Data Preprocessing

For each of the 6 BOLD runs found per subject, the following preprocessing was performed. “First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A deformation field to correct for susceptibility distortions was estimated based on *fMRIPrep*’s *fieldmap-less* approach. The deformation field is that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted (Huntenburg, 2014; Wang et al., 2017). Registration was performed with *antsRegistration* (ANTs 2.3.3), and the process regularized by constraining deformation to be nonzero only along the phase-encoding direction, and modulated with an average fieldmap template (Treiber et al., 2016). Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using *flirt* (FSL 5.0.9, Jenkinson & Smith, 2001) with the boundary-based registration (Greve & Fischl, 2009) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using *mcflirt* (FSL 5.0.9, Jenkinson et al., 2002). BOLD runs were slice-time corrected using *3dTshift* from AFNI

20160207 (Cox & Hyde, 1997; RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following absolute sum of relative motions, (Power et al., 2014) and relative root mean square displacement between affines, (Jenkinson et al., 2002). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., 2014). The three global signals were extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al., 2007). Principal components were estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) were generated in anatomical space. The implementation differs from that of Behzadi et al. in

that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask was obtained by thresholding the corresponding partial volume map at 0.05, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks were resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components were also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values were retained, such that the retained components' time series were sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components were dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e., head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).”

2.4.2 Region-of-Interest Identification

The large-scale canonical networks (i.e., Salience Network [SN], Central Executive Network [CEN], and Default Mode Network [DMN]) involved in the analyses were defined for each participant at spherical regions-of-interest (ROIs) with radii of 5 mm, centered on the coordinates of previously validated regions (C. Li et al., 2019; Menon, 2011). See Figure 4 for a visualization of the ROIs and see Table 2 for a full list of the ROIs and their coordinates.

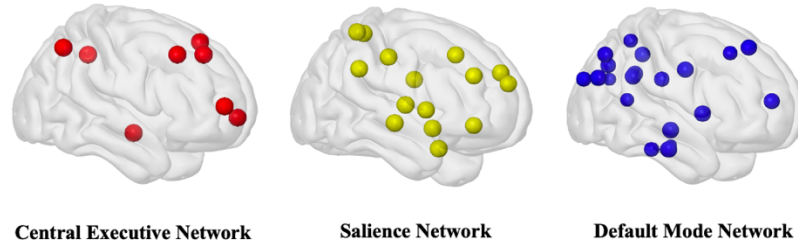


Figure 4: Network Visualization

Table 2: MNI Coordinates of Regions-of-Interest

	Region of Interest	X	Y	Z
SN	Left Middle Frontal Gyrus	-32	45	26
	Left Anterior Insula Cortex	-41	15	-2
	Left Cingulate Gyrus	-2	17	45
	Right Middle Frontal Gyrus	28	43	26
	Right Anterior Insula Cortex	44	13	1
	Left Middle Frontal Gyrus	-40	36	35
	Left Inferior Parietal Louble	-60	-38	35
	Left Precuneus	-9	-56	64
	Right Cingulate Gyrus	11	-29	44
	Right Precuneus	11	-53	63
	Right Inferior Parietal Louble	59	-32	31
	Left Thalamus	-12	0	-21

	Left Posterior Insula Cortex	-40	-16	-3
	Right Thalamus	11	-16	9
	Right Posterior Insula Cortex	39	-13	-7
CEN	Left Dorsolateral Prefrontal Cortex	-35	21	53
	Left Middle Frontal Gyrus	-44	46	-1
	Left Inferior Parietal Lobule	-44	-65	44
	Left Middle Temporal Gyrus	-65	-38	-12
	Left Dorsolateral Prefrontal Cortex	32	26	44
	Left Middle Frontal Gyrus	35	62	7
	Left Inferior Parietal Lobule	46	-54	49
	Left Middle Frontal Gyrus	3	36	44
DMN	Left Posterior Cingulate	-12	-62	10
	Left Middle Frontal Gyrus	-27	-6	59
	Left Culmen	-30	-39	-20
	Left Superior Occipital Gyrus	-36	-88	28
	Right Posterior Cingulate Gyrus	15	-56	13
	Left Precuneus	-6	-61	56
	Right Middle Frontal Gyrus	24	26	47
	Right Culmen	27	-33	-23
	Right Angular Gyrus	43	-79	28
	Left Ventral Posterior Cingulate Gyrus	0	-35	28
	Right Precuneus	0	-76	38
	Left Inferior Parietal Lobule	-39	-64	46
	Right Inferior Parietal Lobule	39	-64	46
	Left Medial Frontal Gyrus	0	49	12
	Left Angular Gyrus	-48	-73	32
	Right Superior Frontal Gyrus	18	38	51
	Left Dorsal Posterior Cingulate Gyrus.	0	-57	30
	Right Ventral Anterior Cingulate Gyrus	0	-17	35
	Right Angular Gyrus	48	-66	29
	Left Thalamus	-6	-6	3
	Left Parahippocampal Gyrus	-24	-37	-9
	Right Parahippocampal Gyrus	24	-21	-23

Note. Coordinates of central point of spherical ROIs, based on definition by Stanford Functional Imaging in Neuropsychiatric Disorders Lab. Table adapted from (C. Li et al., 2019).

2.4.3 Functional Connectivity Analysis

To estimate connectivity as a function of task condition (i.e., anticipation of reward), a correlational psychophysical interaction (cPPI) analysis (Fornito et al., 2012) was utilized. Building on the traditional psychophysical interaction (PPI) model, this technique involves calculating two PPI regressors for each pair of ROIs based on a linear product of each region's time course with the convolved hemodynamic response for the task-based manipulation (e.g., reward anticipation). Partial correlations between cPPI regressors are then computed to quantify covariation in task-related activity, removing variance associated with the original timecourses and the convolved task regressor. To estimate functional connectivity of spontaneous BOLD activity during rest, Pearson's correlations were used. Because variance due to motion was accounted for during preprocessing, motion parameters were not added as covariates in any connectivity analyses.

2.5 Study Measures

2.5.1 Self-Report

Snaith Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS is a 14-item self-report questionnaire that measures hedonic capacity. Participants are asked how much they agree with statements on a scale from 1 ("definitely agree") to 4 ("strongly disagree"). Total scores range from 14 to 56, with higher scores indicating greater levels of anhedonia (i.e., lower levels of hedonic response). The scale showed excellent internal consistency in the current sample (cronbach's alpha = .927).

2.5.2 fMRI Task

Monetary Incentive Delay Task (MID; Knutson et al., 2000). The MID task consisted of five task runs with 24 trials each. Each run lasted approximately 4.5 minutes. As shown in Figure 5, for each trial, participants were presented with one of three possible cue shapes for 500 msec, followed by a fixation crosshair on a computer screen. These cue shapes signaled whether the upcoming trial had the potential for monetary gain (n=40; denoted by “+\$\$”), potential for monetary losses (n=40; denoted by “-\$\$”), or that there was no possibility for monetary gain or loss (n=40; denoted by “0\$\$”). Trial types were presented in pseudo-random order within each run, and runs were counterbalanced across participants.

The cue was followed with a delay of 2250-3750 msec (anticipation period*). Participants were instructed to respond by pressing a button as soon as they were presented with a red square target, which was displayed for a period of 150 msec. Specifically, they were instructed that they could gain or avoid losing money by pressing the button while it remained on the screen. 2400-3900 msec after the target disappeared, participants were notified as to how much money they had gained or lost on that trial, if any.

* A recent neuroimaging meta-analysis showed that, although short, a period of 1500ms is sufficient for detecting a discernable anticipation period during the MID Task (Oldham et al., 2018)

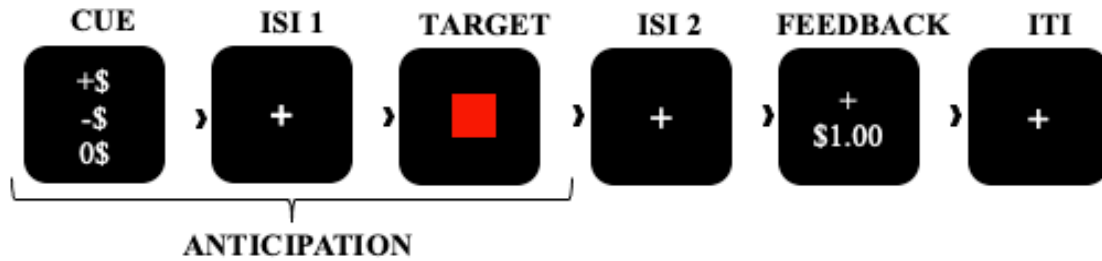


Figure 5: Monetary Incentive Delay Task

Note. ISI = Inter-Stimulus Interval; ITI = Inter-Trial Interval. *Cue* = fixed: 500 ms; *ISI 1* = jittered: 2250 – 3750 ms; *Target* = fixed: 150 ms; *ISI 2* = jittered: 2400 – 2750 ms; *Feedback* = fixed: 1250 ms; *ITI* = jittered to fit task length.

Participants underwent training and practice prior to testing. Task difficulty was based on reaction times collected during the practice session and were selected to allow participants to successfully press the button during target presentation during 70% of trials.

2.5.3 Network Variables

2.5.3.1 Connectivity

To assess connectivity within and between the SN, CEN, and DMN during the anticipation of reward, two measures were utilized and are shown in Figure 6.

Specifically, within-network connectivity (referred to here as within-module degree) indexed connectivity within each of the three networks, and between-network connectivity (referred to here as between-module degree) indexed connectivity between the SN and the CEN and between the SN and the DMN.

$$\text{Within – module degree} = \frac{1}{n} \sum_{i=1}^n \kappa_{iA}$$

$$\text{Between – module degree} = \sum_A^{\text{module } A,B,C\dots} = \frac{\kappa_{iA \cdot B} - \kappa_{S_i}}{\sigma_{\kappa_{S_i}}}$$

Figure 6: Calculated Within- and Between-Network Connectivity Variables

Figure note: κ_{iA} is the sum of all connectivity values for an ROI i within module A , n is the number of ROIs within module A , $\kappa_{iA \cdot B}$ is the sum of all connectivity values for an ROI i between a module A and B , κ_{S_i} is the average of κ over all the nodes in S_i , and $\sigma_{\kappa_{S_i}}$ is the standard deviation of κ in S_i . This within-module degree score measures how well-connected node i is to other nodes within the module, while the between-module degree z-score (z_{iBMD_m}) measures how well connected a node i within module A is to other nodes with another module (B , C , etc.) in the cortical parcellation. A , B , and C modules will correspond to canonical networks: SN, CEN, and DMN.

2.5.3.2 Reorganization

To assess the extent to which each network reorganizes connectivity as a function of brain state, reorganization was calculated using a previously validated technique (Davis et al., 2018) shown in Figures 7 and 8:

$$\text{Reorganization} = 1 - \frac{1}{n \times (n - 1)} \sum_{x \neq y} \rho_{x,y}$$

Figure 7: Calculated Reorganization Variable

Figure note: n is the number of states (e.g., 2 in this case: rest and reward anticipation), and $\rho_{x,y}$ represents the Spearman's correlation between the complex functional connectivity profiles representing two brain states x and y (e.g., functional connectivity matrices representing rest and reward anticipation). Thus, highly correlated matrices represent low reconfiguration (closer to 0), while weakly correlated matrices represent high reconfiguration across task conditions (closer to 1).

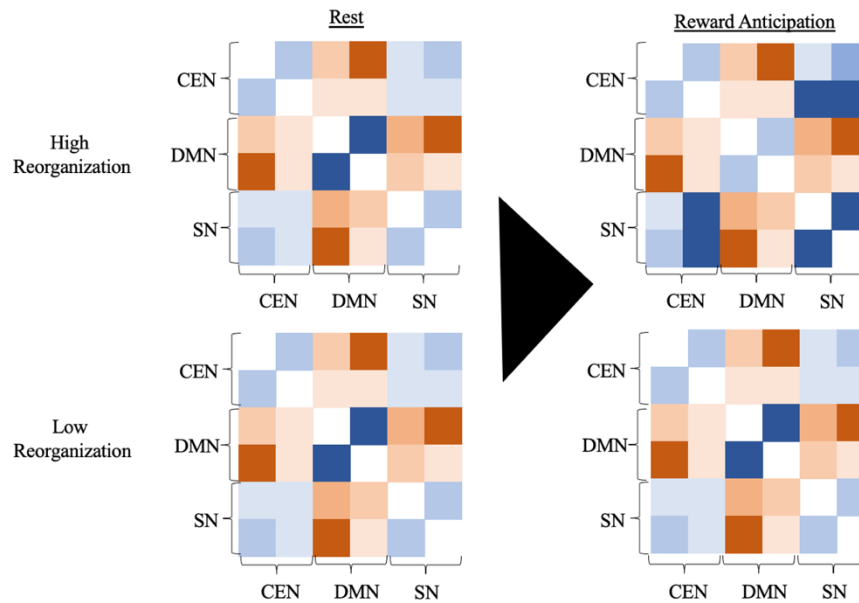


Figure 8: Conceptual Depiction of Network Reorganization

2.6 Data Analysis

2.6.1 Power Analysis

Previous studies have found robust associations between functional connectivity (e.g., between striatal regions and midline cortical structures, between the caudate and cuneus) and measures of anhedonia, with correlation coefficients ranging from $r = 0.25$ to $r = .393$ (Quevedo et al., 2017; Yang et al., 2017). With a Type-I error rate of 5%, the sample size of 77 participants has at least 95% power to detect a small effect size (Cohen's $d = 0.30$).

2.6.2 Within- and Between-Network Connectivity

Indices of within- and between-network connectivity were used to assess network integration during the anticipation of reward. First, within-network connectivity was assessed for nodes within the SN, then between-network connectivity was calculated

between the SN and the CEN, and between the SN and the DMN (totaling three calculated variables). These three variables were entered into a stepwise Multiple Linear Regression model and used to predict anhedonia severity, as measured by the SHAPS.

2.6.3 Network Reorganization

Reorganization values were calculated for the SN, as well as between the SN and DMN and between the SN and CEN. These three values were used in a Multiple Linear Regression model to predict anhedonia severity, as measured by the SHAPS.

To control for the effect of age, age in years was added in at the first step of both (i.e., connectivity and reorganization) models. Only models which denoted statistically significant fit were evaluated.

3. Results

3.1 Task Validation

To ensure construct validity of the MID Task in this clinical sample, behavioral performance (i.e., reaction time) was assessed. As expected, participants responded faster on reward trials ($M = 302.08$ ms, $SD = 55.89$) than on neutral trials ($M = 331.96$ ms, $SD = 53.72$), a statistically significant mean decrease of 29.87 ms, 95% CI [-1.17, -.64], $t(77) = -7.99$, $p < .001$, $d = -0.91$.

Similarly, BOLD signal change in response to reward anticipation versus neutral anticipation was assessed at the group level. As shown in Figure 9, consistent with a recent meta-analysis (Oldham et al., 2018), anticipation of reward during the MID elicited activation in expected frontostriatal regions, including robust activation of the bilateral nucleus accumbens (NAcc). These results suggest that this task is sufficiently rewarding for this clinical sample.

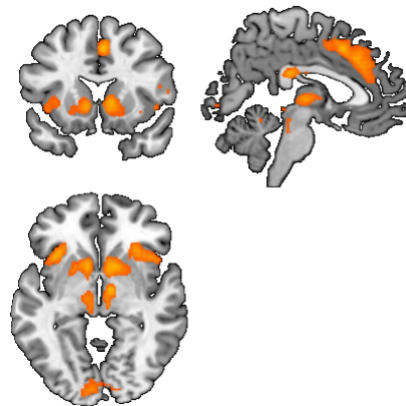


Figure 9: Reward Anticipation > Neutral Anticipation

Note. Group-level activation of reward anticipation > neutral anticipation. Z-statistic image thresholded non-parametrically using clusters determined by $Z > 2.3$, cluster significant threshold of $p = 0.05$.

3.3.1 Task Internal Consistency

Consistent with prior work (Infantolino et al., 2018; Luking et al., 2017), task internal consistency was calculated using split-half reliability. The task was split into two groups by alternating runs (i.e., group 1 consisted of runs 1, 5 and half of run 3; group 2 consisted of runs 2, 4, and the other half of run 3) resulting in two equal halves, each containing 20 reward trials. Mean activation values for each participant were then extracted from the ROIs utilized in this study (i.e., NAcc, and across each of three networks: CEN, SN, DMN). Given that prior work has shown that internal consistency can decrease when utilizing subtraction-based contrasts (Clayson et al., 2021; Infantolino et al., 2018; Luking et al., 2017), internal consistency was calculated for both reward anticipation as well as reward anticipation vs. neutral anticipation contrasts. As shown in Table 3, Spearman-Brown predicted internal consistency coefficients revealed that split-half reliability was acceptable for the task. Consistent with prior work, the reliability for reward anticipation activation was higher than for reward anticipation vs. neutral anticipation, however, the subtraction-based internal consistency was still higher

Table 3: Monetary Incentive Delay Task Internal Consistency

Network/ROI	Anticipation of Reward	Anticipation of Reward > Anticipation of Neutral
	<i>SB</i>	<i>SB</i>
Salience Network (SN)	0.82	0.63
Default Mode Network (DMN)	0.75	0.60
Central Executive Network (CEN)	0.77	0.48
Nucleus Accumbens (NAcc)	0.82	0.52

Note. *SB* = Spearman-Brown predicted internal consistency coefficient.

than previous work has shown in other tasks (i.e., Luking and colleagues [2017] found $SB = 0.36$ for a similar monetary gain and loss task; Infantolino and colleagues [2018] found $SB = .06$ for an emotional face-matching task). Overall, these results suggest that this task showed adequate internal consistency in this sample.

3.2 Reward Anticipation

Given the pronounced role of the NAcc in this task, the relationship between NAcc activation during reward anticipation and anhedonia severity was assessed. No relationship was found between anhedonia severity and activation during reward anticipation* in the NAcc, $r(76) = -0.01, p = 0.96$. Moreover, anhedonia severity was also not related to connectivity between the NAcc and regions of the SN during reward anticipation, $r(76) = 0.04, p = 0.76$. These null associations suggest that anhedonia severity in this sample is not associated with activation in the NAcc nor connectivity between this region and the SN.

3.3 Reward-Related Network Dynamics

3.3.1 Activation

Across both neutral and reward trials, the SN showed greater activation than the CEN and DMN during reward anticipation. Contrasting neutral and reward trials, both the SN and CEN showed significant reward-related increases in activation, whereas the DMN did not show any significant reward-related changes (see Figure 10).

* Results presented here are based on activation extracted from reward anticipation vs. loss anticipation contrast. The results did not change when using activation extracted from the reward anticipation only contrast.

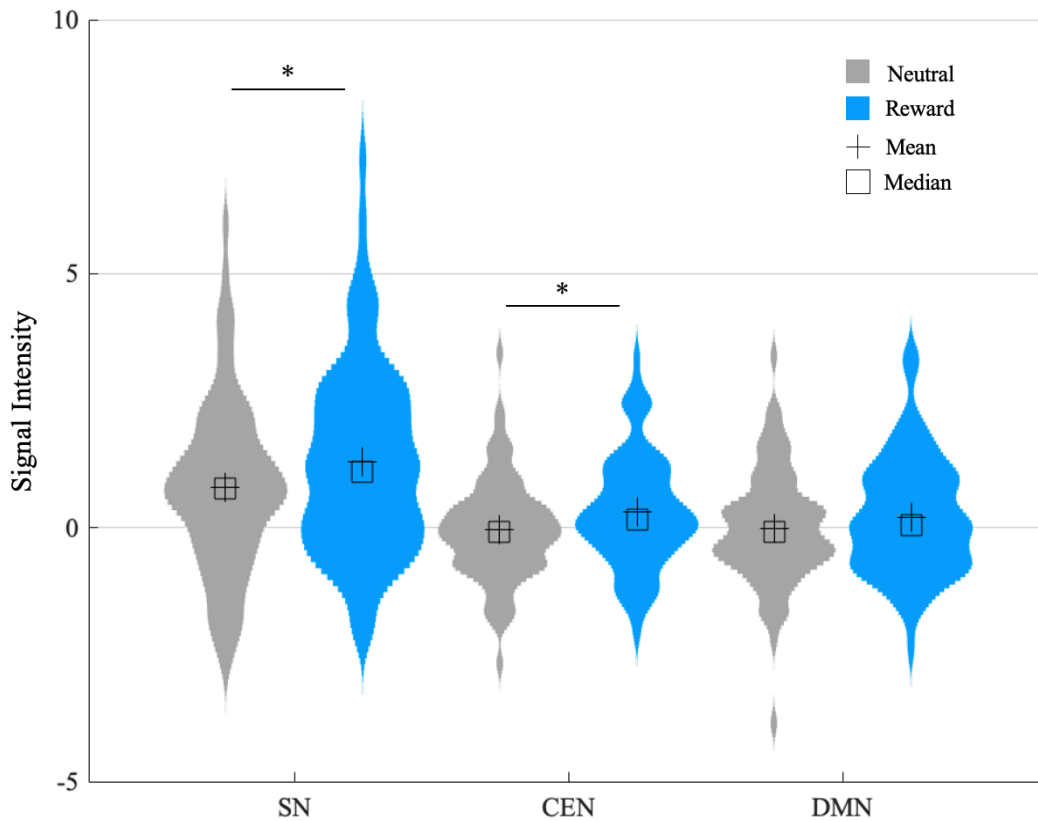


Figure 10: Neutral and Reward Anticipation Activation Across Networks

Note. Task-based activation averaged across ROIs within each network. * = $p < .05$.

3.3.2 Connectivity

Regarding connectivity between these three networks, Figure 11 shows the correlation values characterizing how connected each pair of networks were during reward and neutral trials of the MID, as well as during rest. There was a significant task effect on connectivity such that between-network connectivity across the entire brain was greater at rest (average $r = 0.23$) compared to during task (both neutral and reward trials,

average $r = 0.17$). Although perhaps counterintuitive, a global decrease in functional network connectivity during task relative to rest is consistent with prior literature (Arbabshirani et al., 2013). There were no significant reward-related changes in connectivity (i.e., neutral vs. reward). Importantly, the positive values of the correlations indicate that these three networks show similar patterns of activation under the same conditions, indicating, surprisingly, that the DMN and CEN do not show the expected anticorrelation in this clinical sample.

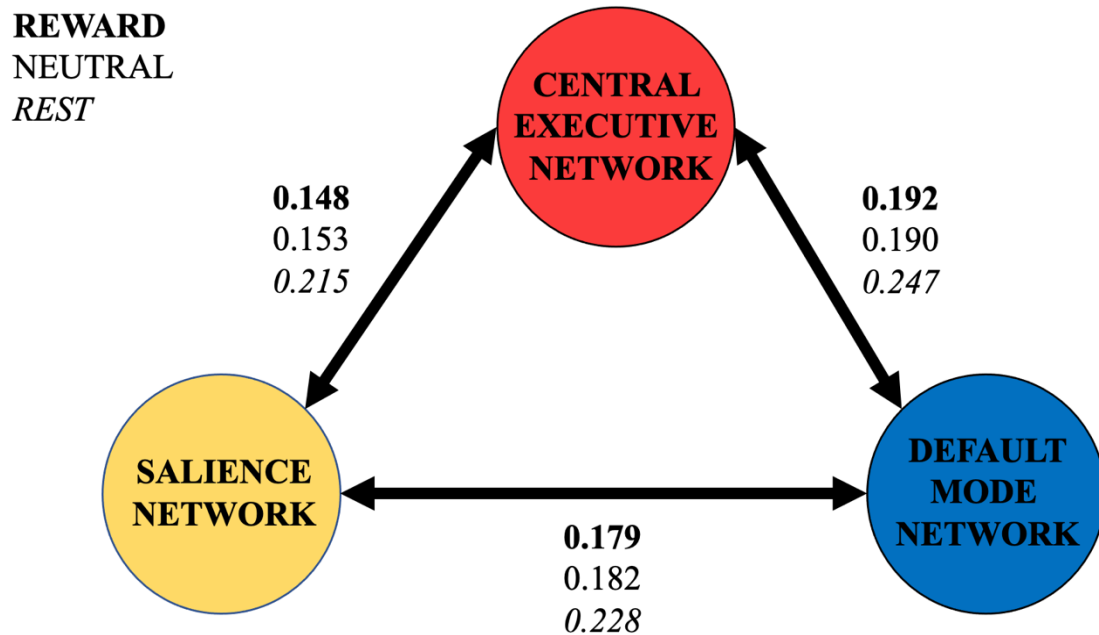


Figure 11: Between-Network Connectivity

Note. Correlation coefficients denoting between-network connectivity. Reward condition = bold, neutral condition = regular, rest = italicized text. No significant state-based differences. No significant reward-related differences (neutral vs. reward), but significant decrease in between-network connectivity from rest to task (both neutral and reward), $p < .05$.

Figure 12 shows within-network connectivity. Similarly to between-network connectivity, there was a significant task effect such that there was greater connectivity between all ROIs within a given network during rest (average $r = 0.29$) than during task (neutral and reward trials; average $r = 0.24$). Also consistent with what was seen in between-network connectivity, no significant reward effects (i.e., neutral vs. reward trials) were observed.

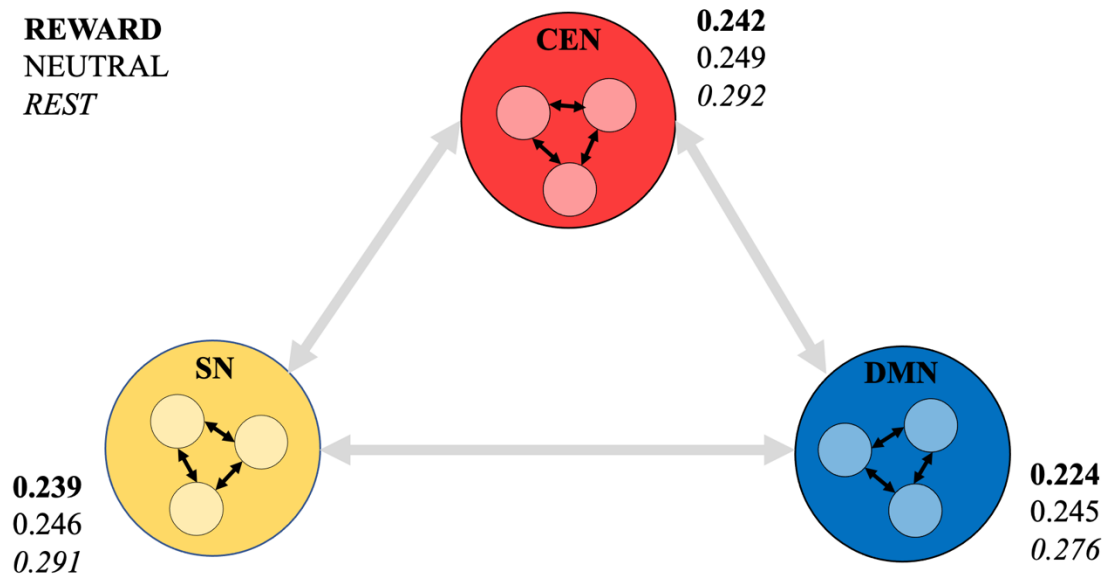


Figure 12: Within-Network Connectivity

Note. Correlation coefficients denoting within-network connectivity. Reward condition = bold, neutral condition = regular, rest = italicized text. No significant reward-related differences (neutral vs. reward), but significant decrease in within-network connectivity from rest to task (both neutral and reward), $p < .05$.

3.3.4 Reorganization

In terms of topographical reorganization between rest and reward anticipation, as illustrated in Figure 13, there was overall more reorganization *between* networks (average reorganization = 0.56) than *within* networks (average reorganization = 0.21). Although there were no significant differences between networks in terms of within-network reorganization, connectivity between the DMN and the other two networks (i.e., CEN and SN) showed significantly less reorganization (average reorganization = 0.55) than connectivity not including the DMN (i.e., between the SN and CEN; average reorganization = 0.58).

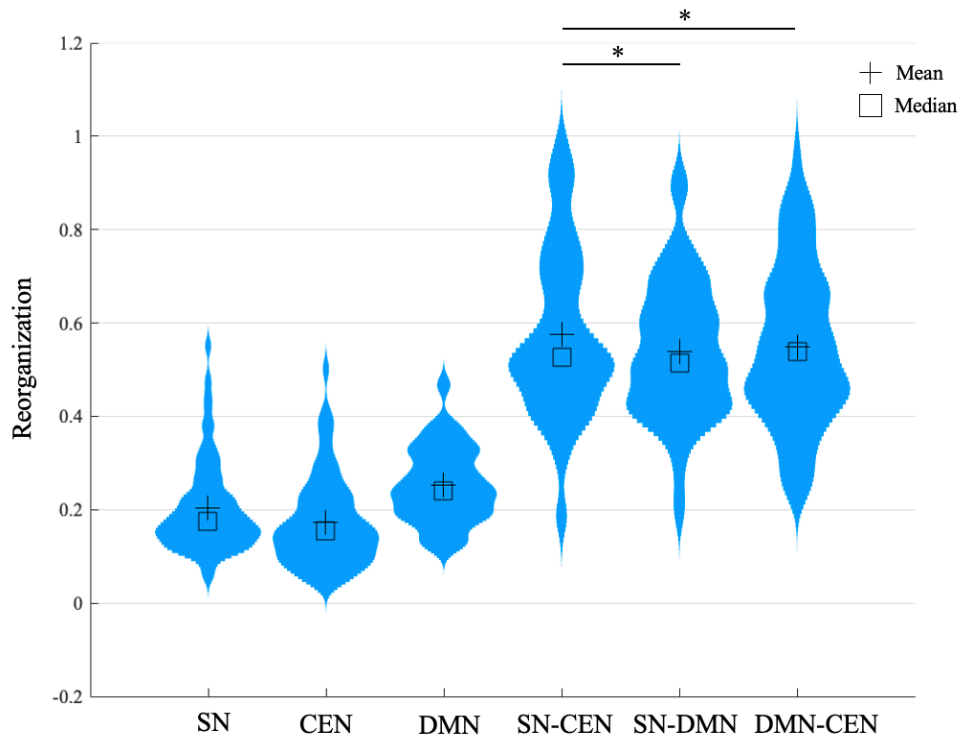


Figure 13: Reorganization Between Rest and Reward Anticipation

3.4 Reward-Related Network Dynamics and Anhedonia

3.4.1 Within- and Between-Network Connectivity

Contrary to predictions, SN connectivity during reward anticipation was not related to anhedonia severity in this sample. Specifically, neither connectivity within the SN, nor between the SN and the CEN or DMN were related to anhedonia severity, $R^2 = 0.03$, $F(1,74) = 0.46$, $p = 0.77$. See Table 4 for full details of the regression model.

Table 4: Multiple Regression Predicting Anhedonia from Network Connectivity During Reward Anticipation

Variable	Anhedonia			
	Model 1		Model 2	
	B	β	B	β
Constant	36.38		35.56	
Age	0.00	-0.07	0.00	-0.05
SN within-network connectivity			-0.43	-0.01
SN – CEN between-network connectivity			-31.60	-0.29
SN – DMN between-network connectivity			29.91	0.27
R^2	0.00		0.03	
F	0.31		0.46	

Note. $N = 74$. No significant predictors. B = unstandardized regression coefficient, β = standardized regression coefficient.

Looking beyond the SN, exploratory analyses assessed whether reward-related within-network connectivity of either the CEN or DMN, or connectivity between the CEN and DMN may predict anhedonia severity. Bivariate Pearson's correlations established that there were no statistically significant associations between anhedonia and connectivity within the CEN, $r(76) = -0.05$, $p = 0.68$, within the DMN, $r(76) = 0.02$, $p = 0.89$, or between the CEN and DMN, $r(76) = -0.03$, $p = 0.77$. Overall, within- and

between-network connectivity of the SN, CEN, and DMN during reward anticipation did not relate to anhedonia in this sample.

3.4.2 Reorganization

Moreover, the magnitude of topographical changes (i.e., reorganization) that took place within and between the SN during the transition from rest to reward anticipation also did not relate to anhedonia severity in this sample. Specifically, as shown in Table 5, neither reorganization of the SN, nor reorganization between the SN and the DMN or between the SN and the CEN when transitioning between rest and reward anticipation predicted anhedonia severity in this sample, $R^2 = 0.10$, $F(1,67) = 1.68$, $p = 0.17$.

Table 5: Multiple Regression Predicting Anhedonia from Network Reorganization Between Rest and Reward Anticipation

Variable	Anhedonia			
	Model 1		Model 2	
	B	β	B	β
Constant	36.06		39.16	
Age	0.00	0.01	0.00	0.00
SN reorganization			5.14	0.07
SN - CEN reorganization			13.72	0.36
SN - DMN reorganization			-24.43	-0.52
R^2	0.00		0.10	
F	0.23		1.68	

Note. $N = 74$. No significant predictors. B = unstandardized regression coefficient, β = standardized regression coefficient.

To assess reorganization beyond the SN, exploratory analyses tested whether reorganization of the DMN or CEN from rest to reward anticipation may impact anhedonia severity. Bivariate Pearson's correlations established that there was not a significant association between anhedonia severity and reorganization within the CEN, $r(68) = -0.08$, $p = 0.49$ or between the CEN and DMN, $r(68) = -0.22$, $p = 0.08$. However, as shown in Figure 14, there was a significant linear relationship between reorganization within the DMN and anhedonia severity, $r(68) = -0.29$, $p = 0.02$, such that less reorganization from rest to reward anticipation was associated with greater anhedonia severity.

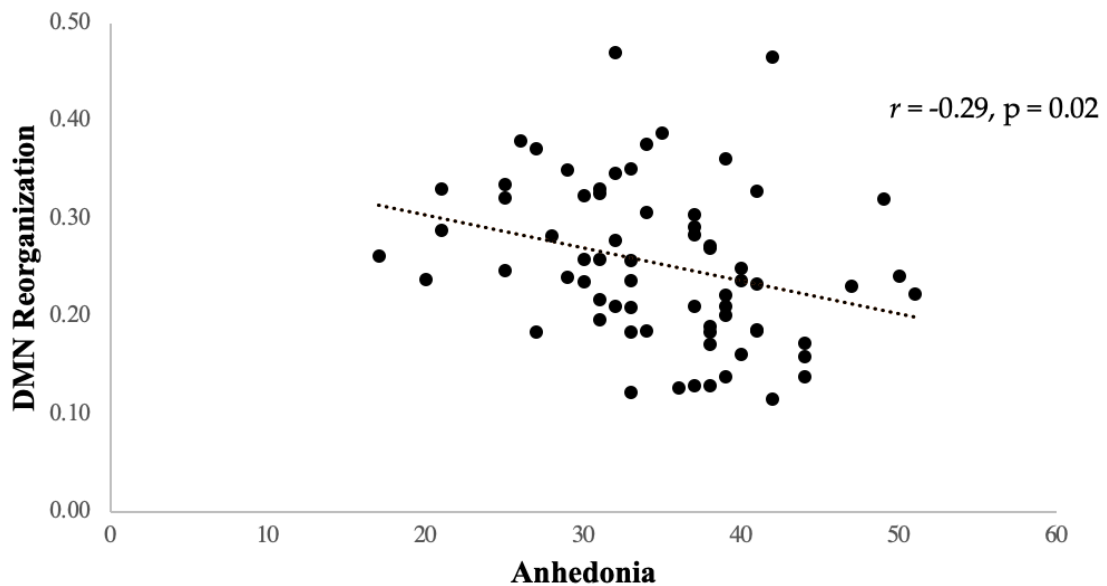


Figure 14: DMN Reorganization and Anhedonia

Note. Significant correlation between anhedonia severity and reorganization within the DMN when transitioning between rest and reward anticipation and anhedonia severity.

This association remained significant after controlling for the effect of age, $r_{\text{partial}}(65) = -0.29$, $p = 0.02$, as well as depression severity, $r_{\text{partial}}(65) = -0.27$, $p = 0.03$. To ensure that this effect was related to reward anticipation rather than task overall, a bivariate Pearson's correlation ensured that there was not a significant relationship between anhedonia and reorganization of the DMN from rest to neutral anticipation, $r(68) = -0.17$, $p = 0.16$. To further characterize how the DMN may be reorganizing between these states, within-network connectivity of the DMN at rest relative to during reward anticipation was assessed. As illustrated in Figure 15, this sample showed significantly less connectivity within the DMN during reward anticipation ($M = 0.23$, $SD = 0.08$) compared to rest ($M = 0.28$, $SD = .09$); $t(70) = 5.35$, $p = 0.00$.

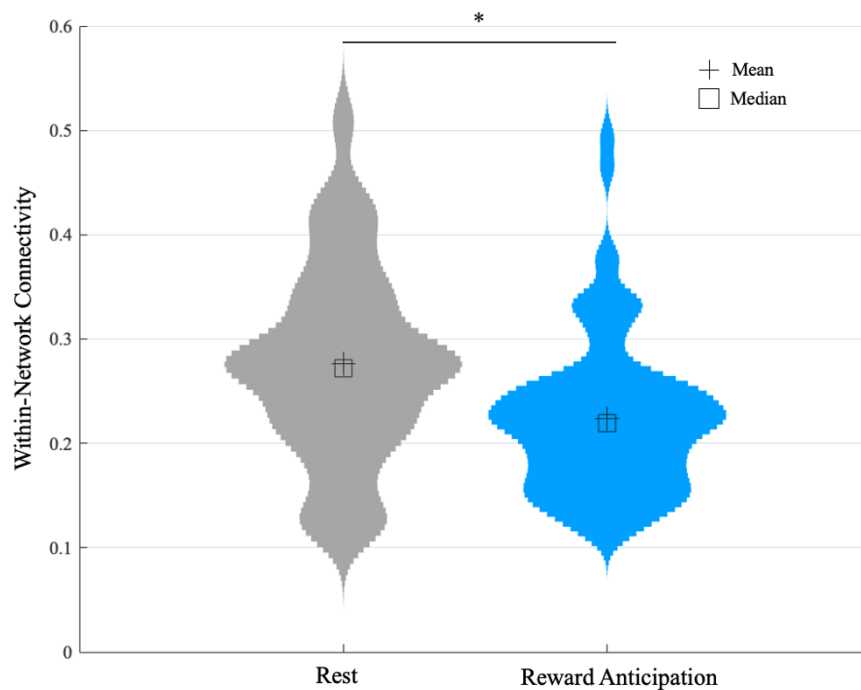


Figure 15: DMN Within-Network Connectivity

Taken together with the earlier finding that reorganization scores in this network declined with increasing anhedonia (Figure 14), these results suggest that the shift between resting and reward states is impaired as anhedonia becomes more severe.

4. Discussion

This study aimed to assess state-based network dynamics in a transdiagnostic sample of adults with clinically significant anhedonia. Two fundamental gaps in the clinical neuroscience of anhedonia were addressed. First, consistent with RDoC, anhedonia was assessed in a clinical, transdiagnostic sample. Second, two multivariate connectivity measures were utilized: network connectivity during reward anticipation, as well as network reorganization when transitioning between rest and reward anticipation states. Hypotheses centered on the role of the SN in anhedonia, and therefore the primary analyses assessed these measures with regard to the SN and the SN's connectivity with the CEN and the DMN. Exploratory analyses examined the possibility that anhedonia severity may instead be associated with network dynamics of the DMN and CEN.

4.1 Salience Network

Given existing research supporting the role of reward processing in anhedonia, the underlying hypothesis of this study was that anhedonia severity would be related to saliency-mapping processes. However, results from this study do not support this assumption. Anhedonia severity in this sample was not associated with (1) reward-related activation in the NAcc, (2) reward-related connectivity between the NAcc and the SN, (3) reward-related connectivity within the SN, (4) reward-related connectivity between the SN and the DMN or CEN, (5) reward-related reorganization of the SN, or (6) reward-related reorganization of connectivity between the SN and CEN or DMN.

This broad array of null findings, across multiple levels of analysis, presents compelling evidence that in adults with clinically significant anhedonia, deficits in

saliency-mapping may not contribute to individual differences in clinical severity. These findings do not, however, rule out the potential for saliency-mapping processes to play a role in anhedonia holistically. Anhedonia-related deficits in the saliency-mapping system may only be detectable when including individuals with a full range of anhedonia, rather than just those with clinically significant anhedonia, or only when comparing a sample of individuals with anhedonia to an affectively healthy sample. Nevertheless, the present findings do challenge the notion that anhedonia severity is driven by reward-related changes in connectivity within the SN, and between the SN and the other networks.

4.2 Default Mode Network

Surprisingly, the DMN played a more integral role than the SN in anhedonia severity in this sample. Specifically, anhedonia severity was negatively associated with the magnitude of reorganization that took place within the DMN when transitioning between rest and reward anticipation. Hypothetically, active engagement (e.g., of the reward system), compared to rest, requires dynamic reconfiguration of neural networks to enhance performance. One example of this is active disengagement of task-unrelated networks (in this case, the DMN) in order to facilitate efficient cognition (Weissman et al., 2006). Broadly speaking, higher levels of reorganization of brain networks are thought to represent cognitive flexibility and are associated with more successful performance on cognitive tasks in healthy populations (Braun et al., 2015; Davis et al., 2018; DeSalvo et al., 2014; Spielberg et al., 2015). The ability of brain networks to flexibly reorganize based on context is critical to goal-directed behavior, and research has

shown that this reorganization can be captured when comparing task to resting state brain scans (Di et al., 2013).

Although unexpected, the relevance of the DMN in the context of anhedonia is consistent with work showing anhedonia to be characterized by a lack of responsivity in the DMN; individuals with high levels of anhedonia exhibit less DMN deactivation in response to positive images compared to neutral (Guo et al., 2016). Moreover, in a study examining intra-DMN connectivity, Zhang and colleagues showed anhedonia to be related to insufficient DMN decoupling during reward expectancy (2017). Importantly, these studies examined anhedonia in depressed samples. The findings from the present study in a transdiagnostic anhedonic sample, which remained significant even after controlling for depressive symptoms, build on past findings and suggest that this lack of DMN sensitivity may be uniquely related to anhedonia.

Another important characteristic of this sample was that all three canonical networks appeared to operate in unison – both during task as well as during rest. The CEN and DMN exhibiting coupled connectivity is in contrast to a substantial body of literature suggesting that the CEN and DMN are anticorrelated in healthy adults (Fox et al., 2005). This anticorrelation is thought to facilitate switching from internally (DMN) to externally (CEN) oriented focus in order to stay on task and achieve goals in the external world. However, when a goal is internally focused, rather than externally, (e.g., focused creative thinking, mind wandering, autobiographical memory retrieval, mental simulation), these two networks may cooperate (Beaty et al., 2016; Christoff et al., 2009; Gerlach et al., 2011; Konishi et al., 2015; Spreng & Grady, 2010). The consistent parallel

functioning of these two networks across both rest and task states may indicate that individuals in this sample tended to be internally focused in a goal-oriented manner, and that the external goal of pushing the button to receive a potential monetary reward was not sufficient to disengage from their internal world and orient to the external.

The positive correlation between the CEN and DMN (Figure 13) plus the observed association between reorganization of the DMN in response to potential rewards and anhedonia severity (Figure 14) suggest that individuals in this sample may have difficulty flexibly adapting attentional resources from their internal world to the external world. One reason that individuals with anhedonia may have difficulty shifting from internal to external focus may be a lack of motivation to perform well. However, in the present sample this does not appear to be the case as a lack of motivation would likely be indexed by saliency-mapping or more speeded behavioral responses on reward trials, which were both unrelated to anhedonia severity. Moreover, the sample overall showed faster response times and greater NAcc activation on reward trials relative to neutral, suggesting that the sample as a whole was responsive to the potential reward.

What cognitive process may be keeping these individuals stuck in their internal worlds? Any interpretation is necessarily limited by the paucity of research on the subjective experience of, and internal cognitive processes specific to, anhedonia as opposed to other related clinical presentations. In the context of depression, for example, rumination and overgeneralization of autobiographical memories are key cognitive processes which implicate an overly dominant DMN (Hamilton et al., 2015; Zheng et al., 2015). Decreased connectivity of the DMN has also been implicated in posttraumatic

stress disorder. Specifically, hypoactivity of the DMN, as well as weakened connectivity between the DMN and CEN, is associated with increased severity of posttraumatic stress disorder and is thought to reflect phenomenological processes such as intrusive symptoms, re-experiencing, dissociation, and fear generalization (Akiki et al., 2017; Bluhm et al., 2009; Viard et al., 2019). In schizophrenia, deficits in DMN suppression during tasks has been attributed to cognitive symptoms present in the disorder such as hallucinations, delusions and disorganized thinking (Schneider et al., 2011).

Interestingly, there is some emerging evidence that mind-wandering, a cognitive process of attending to thoughts unrelated to external stimuli which is largely associated with the DMN (e.g., Poerio et al., 2017), may be a prominent cognitive feature of anhedonia. Webb and colleagues found that rates of mind-wandering were higher in a group of anhedonic versus psychiatrically healthy adolescents, and that this was associated with deficits in DMN-SN connectivity (Webb et al., 2021). Moreover, mind-wandering has also been shown to recruit, collaboratively, the DMN and the CEN, with the recruitment of the CEN and DMN being most pronounced when participants were engaging in mind wandering outside of their meta-awareness (i.e., they were not aware that their attention was focused inward and not on the present moment; Christoff et al., 2009). It is possible that for individuals with anhedonia, the lack of salient reinforcers tethering them to the present moment creates the perfect circumstances under which their minds can spontaneously wander. Applying the present findings to this hypothesis would suggest that individuals with more severe anhedonia would be more prone to mind-wandering.

Regardless of where the mind “goes” during these periods, if an individual is predominantly internally focused, it is far less likely that they will come into contact with naturalistic reinforcers. It is therefore possible that this hyposensitivity of the DMN is a key maintaining factor for anhedonia. For example, if an individual experiencing anhedonia is able to behaviorally activate themselves enough to attend a social gathering but is too caught up in their internal world, they may miss out on opportunities for social connectedness and shared positive affect. In turn, no reward learning would take place, and there would be no added impact on future anticipation and/or motivation to engage socially.

4.3 Clinical Implications

Although uncertainty remains regarding what internal cognitive process may be taking place, results from the present study suggest that potential treatments should focus on increasing the sensitivity of individuals to cues in their external world. Put another way, individuals with anhedonia may benefit from treatments that focus on bolstering their ability to flexibly shift attention from their internal to external experience.

4.3.1 Mindfulness

Mindfulness, or purposefully paying attention to the present moment in a nonjudgmental manner (Kabat-Zinn, 1982), has been shown to significantly impact DMN functioning (Berkovich-Ohana et al., 2012; Brewer et al., 2011; Doll et al., 2015; Hölzel et al., 2011). In fact, two recent studies have examined how mindfulness training impacts the relationship between the CEN and DMN. A randomized controlled trial found that 12 weeks of Mindfulness Based Cognitive Therapy (MBCT) reestablished the

anticorrelation between the CEN and DMN in a sample of patients with bipolar disorder (Chou et al., 2022). Another study found that mindfulness training increased the magnitude of the anticorrelation between the DMN and CEN in children (Bauer et al., 2020). Moreover, in an ongoing clinical trial examining MBCT as a treatment for transdiagnostic anhedonia, interim findings showed that reductions in connectivity within the DMN, and between the DMN and CEN were associated with improvements in anhedonia (Cernasov et al., 2021b). Choosing to guide one's attention repeatedly and nonjudgmentally back to the present moment during formal mindfulness practice holds great promise as a non-invasive and cost-effective treatment for enhancing the ability of individuals with anhedonia to flexibly shift from their internal to external worlds.

4.3.2 Non-invasive Neuromodulation

Methods of non-invasive neuromodulation, such as repetitive transcranial magnetic stimulation (rTMS), deliver repeated magnetic pulses to specific brain regions and have been shown to have impacts that extend beyond these target regions to entire brain networks (To et al., 2018). Of particular relevance to the findings from this study, two groups have shown that excitatory rTMS of regions of the CEN (i.e., posterior middle frontal gyrus, left dorsolateral prefrontal cortex) can induce an anticorrelation between the CEN and DMN (Chen et al., 2013; Liston et al., 2014). In a promising new naturalistic study, TMS of one of the same regions of the CEN (i.e., left dorsolateral prefrontal cortex) was found to significantly reduce anhedonia in a depressed sample (Fukuda et al., 2021). However, this study did not utilize concurrent or pre-post

neuroimaging, so it remains unknown specifically what impact this TMS had and how it maps on to clinical improvement.

Looking beyond the traditional target of the CEN, an alternative approach may be suggested by the present results. Specifically, applying inhibitory neuromodulatory treatment (i.e., continuous Theta Burst Stimulation) to regions of the DMN to actively disengage the DMN (e.g., Hermiller et al., 2020) may be particularly effective in targeting anhedonia.

4.4 Limitations

These findings are not without limitations. First, the clinical applications of these findings are constrained by the lack of control group as well as a narrow overall range of anhedonia scores. However, because the sample is representative of the larger population of anhedonic adults who would benefit from treatments specific to this clinical presentation, these findings do hold great promise for identifying neurobiological treatment targets.

As a clinical condition, anhedonia is best assessed by asking patients about their experience of their symptoms. Most often in research studies, including the parent study, this is done through self-report questionnaires. Although the SHAPS is currently the gold-standard self-report assessment of anhedonia, it is limited in the facets of anhedonia that it captures. While the SHAPS focuses on overall hedonic experience, it does not independently capture different components of anhedonia such as anticipation of reward, consummatory pleasure, or ability to learn from rewards.

The duration of the resting-state scan (approximately 5 minutes) is modest relative to recommendations that at least 12 minutes of resting-state data are needed to maximize test-retest reliability (Birn et al., 2013). Because the parent study has task and resting-state data, one potential next step is to combine across these conditions to assess general functional connectivity (Elliott et al., 2019).

Finally, recent work (Marek et al., 2022) has questioned the reproducibility of studies associating clinical symptoms with neuroimaging data (i.e., brain-wide association studies; BWAS). The authors argue that BWAS effects are so small that sample sizes in the thousands are necessary to meet replication standards. This is undoubtedly an important consideration, and future replications of this work should aim to do so in larger sample sizes. However, present study did utilize two methods that Marek and colleagues suggest may make findings more reliable: intervening on, as opposed to observing, the brain (i.e., task-based activation) and the utilization of a multivariate approach.

5. Conclusions and Future Directions

This is the first study, to date, to examine network dynamics in a transdiagnostic sample of adults with anhedonia. Building on earlier work, this study leveraged advanced neuroimaging processing (i.e., *fMRIprep*) and analytic techniques (i.e., multivariate, graph theoretical analysis) to capture how macroscale brain networks respond to reward anticipation in this sample. The primary motivation for this study was to utilize neuroscientific measures to inform clinical treatment targets. Contrary to the hypotheses, results from this study suggest that anhedonia severity is not related to saliency-mapping processes (i.e., within- and between-network connectivity or reorganization of the SN), but instead to an inability of the DMN to flexibly adapt to external stimuli. More specifically, in this sample, individuals with more severe anhedonia had more difficulty disengaging from internally oriented thought in the context of salient external stimuli.

Understanding the cognitive manifestations of the observed hyposensitive DMN is an important next step in enhancing the clinical implications of the present study. Ecological Momentary Assessment is a promising avenue through which researchers may assess these cognitive processes in real-time outside of the laboratory context. Questions such as “Were you thinking about something related to what you were doing?”, “Were you thinking about something pleasant, unpleasant, or neutral?”, and “Were you thinking about something in the future, past, or neither?” which Webb and colleagues utilized in their 2021 study assessing mind-wandering in adolescents hold great promise for gaining clarity around the cognitive phenomenology of anhedonia.

Combining more subjective measures with neuroimaging will also be important. For example, asking research participants “What were you thinking about?” following a resting-state scan, and “How engaged did you feel with the task you just completed?” or “Did you notice you were thinking about anything other than the task? If so, what?” following fMRI tasks.

Another important next step will be parsing the different subsystems of the DMN in the context of anhedonia. Extant work has shown that the DMN can be subdivided into two subsystems: anterior and posterior, and that each subsystem has slightly different functionality (Damoiseaux et al., 2008; Knyazev, 2013). Of particular relevance to the present findings, the posterior DMN has been implicated in predominantly unconscious processes including emotion and salience detection (Husain & Nachev, 2007; Iidaka et al., 2001). How these two subsystems do or do not work together in the context of anhedonia, and if one subsystem tracks more closely with severity of anhedonia will add important specificity to the present findings.

Overall, the findings from the present study shed important light on a network that has yet to be conceptualized as relevant in anhedonia: the DMN. In this way, these findings elucidate the potential role of internal cognitive processes in anhedonia. Increased clarity regarding the subjective experience of anhedonia and, more specifically, the cognitive thought patterns that may keep individuals with anhedonia engaged in their inner world, holds great promise for helping individuals suffering from anhedonia.

Appendix A: List of Abbreviations

List of Abbreviations

BOLD	blood oxygen level dependent
BWAS	brain-wide association studies
CEN	central executive network
cPPI	correlational psychophysical interaction
dACC	dorsal anterior cingulate cortex
DMN	default mode network
DSM-IV	Diagnostic and Statistical Manual - version IV
fMRI	functional magnetic resonance imaging
ISI	inter-stimulus interval
ITI	inter-trial interval
KOR	κ opioid receptor
MBCT	Mindfulness Based Cognitive Therapy
MID	Monetary Incentive Delay Task
MINI	Mini International Neuropsychiatric Interview
MRI	magnetic resonance imaging
NAcc	nucleus accumbens
NIMH	National Institute of Mental Health
PTSD	post-traumatic stress disorder
RDoC	Research Domain Criteria
ROC	receiver operating characteristic
ROI	region of interest
rTMS	repetitive transcranial magnetic stimulation
SHAPS	Snaith Hamilton Pleasure Scale
SN	saliency network
TMS	transcranial magnetic stimulation
VS	ventral striatum
VTA	ventral tegmental area

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Biography

Angela Pisoni is a 6th year student in the clinical psychology doctoral program at Duke University, working under the mentorship of Dr. Moria Smoski in the Psychology of Emotion, Anhedonia and Reward Lab. Angela received her bachelor's degree in psychology, with a minor in Italian studies, from Brandeis University in 2012. She received her master's degree in clinical psychology from Duke University in 2019.

Angela has co-authored 11 peer-reviewed publications, listed below. In 2020, Angela was awarded a Ruth L. Kirschstein Institutional National Research Service Award (NRSA) from the National Institute of Mental Health to fund her dissertation work. During her time at Duke, she has also received five Summer Research Fellowships, and three travel awards to attend academic conferences. As the final step toward completion of her PhD in Clinical Psychology from Duke University, Angela will complete her pre-doctoral clinical internship training at the Durham Veterans Affairs Medical Center during the 2022-2023 academic year.

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