8-18-2022 10:00 AM

Role of the default-mode network during narrative integration in major depressive disorder

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Psychology

Abstract

How brain activity is synchronized across individuals during narrative comprehension has previously been characterized by functional magnetic resonance imaging (fMRI) in healthy and patient populations. To our knowledge, there has been limited investigation as to how it is affected by major depressive disorder (MDD). We addressed this issue with fMRI through examination of inter-subject synchronization in the default mode network (DMN), brain structures which have previously been implicated in MDD pathology. Twenty-two patients with MDD and 20 matched control participants listened to Intact versus Scrambled versions of an auditory narrative; these experimental conditions differed in the degree of temporal integration they demanded. Across conditions, we found a significant increase in synchrony within DMN for intact narratives. As compared to controls, patients demonstrated a significant increase in synchrony across multiple DMN regions, some specific for intact narratives. Our findings highlight the impact of brain abnormalities in MDD on an ecologically relevant cognitive function.

Keywords

fMRI, depression, default mode network, narrative processing, intersubject correlation, recall, memory, executive function

Summary for Lay Audience

How we take in and make sense of information is key to how we interact with the world around us. When we listen to a story, the way the brain integrates it is similar between people. We take different senses together and bind them in levels which pass along information as they become more complex. Therefore, we can study this process by measuring how similar activity is in different brain regions when participants are listening to a story and when the story is disrupted. Previous studies found that areas of the default mode network play a key role in making sense of stories. Researchers used the story 'Pie-man,' in healthy and some patients but it is unknown in patients with depression. Those with depression have difficulties related to changes in the brain involved in story processing. The goal of this study was to examine if those differences would impact how the story is processed. We scanned 22 clinically depressed patients and 20 controls in functional magnetic resonance imaging while they listened to Intact and Scrambled story. By changing the amount of information presented, we can see if the brain signal is consistent with others scanned. When information is disrupted, we found that patients with depression showed a similar change to controls. However, folks with depression showed a higher consistency in some regions compared to controls. Overall, we showed a difference in how the brain processes stories differently in depression. These findings shed a new light on how information processing is affected by depression. This could inform treatments which target the affected brain area.

Co-Authorship Statement

The work presented in this thesis was carried out in collaboration with Mahdieh Varvani Farahani, Dr. Ali Khan, and Dr. Stefan Köhler, with Dr. Köhler supervising the overall project.

Dr. Köhler contributed significantly to the background research, motivation, and interpretation of the results for the current project. He also coordinated efforts from collaborators including Dr. Janice Chen who provided the experimental design and initial scripts used to calculate intersubject correlations. The code and data analyses were written by Darren, with reused code from Dr. Chen to suit this data. Dr. Köhler offered significant suggestions and edits to the content and clarity of this thesis.

Dr. Khan contributed to the scanning protocol and imaging processing pipelines used to analyze functional and structural images. Dr. Khan and Dr. Ingrid Johnsrude suggested preprocessing analysis steps and guided discussion on potential methods and ways to improve data analyses.

Sudesna Chakraborty, and Mahdieh Varvani Farahani contributed significantly to the project initialization and data collection, with additional assistance from Annie Wu. Sudesna Chakraborty, and Mahdieh Varvani Farahani, Georgia Gopinath, and Nardeen Yalda additionally aided in scoring of the neuropsychological measures used to describe the participant characteristics.

Acknowledgments

Thanks to everybody in the Köhler lab for the continuous support and constructive feedback throughout my time despite the challenges that COVID presented upon my arrival. Thank you to Dr. Köhler for his constant guidance, encouragement, and feedback throughout my thesis work.

Thank you to Mahdieh Varvani Farahani, Sudesna Chakraborty, and Kayla Mae Ferko who assisted in various parts of the project before me and helped me get situated into the new environment especially during these challenging times.

I am thankful to the staff, faculty, and students at the Brain and Mind and the Centre for Functional and Metabolic Mapping for creating such a collaborative environment and to always lend a helping hand in discussing how to improve our work.

Thank you to my parents, Ru De Liang and Shu Bing Su, for instilling a can-do mindset and encouraging me to pursue higher education. Thank you to my girlfriend, Glendy Yip for being there for me from long distance, helping me read my thesis, and generally putting up with me despite this being a limited field of knowledge. Unfortunately, my grandmother, Qin Huan Chen, passed away just prior to the completion of this thesis, but I hope that she will rest well knowing that we now have a first-generation graduate student in the family.

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Chapter 1

1 Introduction

Major depressive disorder (MDD) is one of the most common mental health disorders and the United States alone had an estimated impact on 8.4% of its adult population in 2020 (Center for Behavioral Health Statistics and Quality, 2021). With acute triggers, for instance recent events like COVID-19, the estimated prevalence of depression in both the United States and worldwide has risen to potentially 25% (Bueno-Notivol et al., 2021; Ettman et al., 2020). Depression is a complex disorder and our understanding about how it affects cognitive processing has both expanded and shifted over the past 30 years (Richards, 2011). As cognitive neuroscientists, we are focused on understanding how any behavioral, cognitive, and affective abnormalities are related or reflected in the brain, a topic which I will expand on in subsequent sections. An area of study which has significantly increased our understanding of MDD utilized functional magnetic resonance imaging (fMRI) to characterize network level abnormalities in the default mode network (DMN) (Grimm et al., 2009; Marchetti et al., 2012; Peng et al., 2015; Sheline et al., 2009; X. Zhu et al., 2012). While the DMN has been extensively studied in depression, most prior work has focused on resting-state functional connectivity. The present project aims to further our understanding of the functional contributions of the DMN and its impact on depression in other states. Towards this end, I will use naturalistic stimuli involving a narrative and intersubject correlation of fMRI Blood Oxygenation Level Dependent (BOLD) signal to explore the consistency of DMN contributions in patients with MDD as compared to control participants. The use of this novel method has had limited exploration in MDD thus far. However, it holds a unique promise as it allows us to explore the engagement of the DMN during an experimentally controlled cognitive state and to determine how both neural signals and behavior are impacted by the presence of MDD.

1.1 Major Depressive Disorder

Depression is classified as an affective disorder but also includes cognitive symptoms. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) diagnosis of MDD requires an individual to present with at least 5 of the 8 emotional, cognitive, or physical symptoms for a minimum of 2 weeks, and not otherwise attributed to other medical conditions (American Psychiatric Association, 2013). The symptoms must include either (1) depressed mood or (2) loss of interest, but any combination of (3) weight change, (4) slowed thought or movement, (5) fatigue, (6) feelings of worthlessness or guilt, (7) diminished thought processing, and (8) recurrent thoughts of death (American Psychiatric Association, 2013). Over the years, the criteria for diagnosis of the disorder have been transformed, but also our knowledge of observable behavioral symptoms has increased exponentially since the early classification in former DSM editions (Richards, 2011). Longitudinal studies which monitored the natural course of the disease provided consensus on how MDD was defined (Katz et al., 1979). Nevertheless, the condition of MDD is difficult to study in isolation due to the high comorbidity rates with other disorders including anxiety (Richards, 2011). While treatments have been effective at providing symptom alleviation or improvement, patient outcomes vary based on responses (Mann, 2005). Most treatments are pharmacological in nature, including monoamine oxidase inhibitor (MAOI), selective serotonin reuptake inhibitor (SSRI), noradrenaline (norepinephrine) reuptake inhibitor (NARI), dual-action agent combinations of SSRI and NARI formally tricyclic-based, and adrenergic autoreceptor blocking agents (Kupfer et al., 2012). In treatment resistant cases, however, brain stimulation-based treatments are also offered, such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) (Mann, 2005). Differences in effectiveness of treatments are to some extent due to variability in brain abnormalities found in MDD.

1.1.1 Brain abnormalities revealed by neuroimaging

MRI has made headways in the investigation of pathological changes to provide objective evidence that brain alterations are associated with MDD. Both structural and functional studies have refined our understanding of the neurocircuitry involved and have aided in the identification of regions for targeted treatment (F. F. Zhang et al., 2018). Major

regions of focus include the prefrontal cortex, which is thought to be responsible for emotional regulation, and the hippocampus, which is essential to learning, memory, and context dependent emotional responses (Palazidou, 2012).

Extensive reviews of MRI studies have revealed volumetric reductions in frontal regions of the anterior cingulate, orbitofrontal cortex, and prefrontal cortex, and subcortical or allocortical regions such as the hippocampus, putamen, and caudate nucleus (Koolschijn et al., 2009). The regulation of the frontal lobes and regions of the amygdala, ventral striatum, medial prefrontal and anterior cingulate cortical regions, and lateral prefrontal cortical systems that are impacted in MDD are likewise significantly affected by the presence or absence of the specific neurotransmitters, including serotonin and dopamine (Kupfer et al., 2012). However, some structural deficits may be reversible as neurogenesis in the hippocampus in patients with MDD has been found following pharmacological and ECT treatment, which resulted in both structural and behavioral improvements (Palazidou, 2012; F. F. Zhang et al., 2018). The frontal cortex and hippocampus show the most consistent volumetric reductions in MDD, and these regions are furthermore functionally connected.

A review of functional positron emission tomography (PET) studies corroborated the impacts of regions with volumetric deficits with functional increases in glucose metabolism in the right subgenual and pregenual anterior cingulate cortices (Sacher et al., 2012). However, in resting-state, treatment, and emotional activation studies, there are varied increases and decreases in activation across the regions of the frontal cortex, insula, superior temporal gyrus (STG), basal ganglia, and cerebellum (Fitzgerald et al., 2008). These systemic alterations in the presence of MDD are further key as focal changes lead to widespread impacts in larger neural networks.

The perspective that neural networks are disrupted in MDD is gaining increased acceptance in scientific literature. In both task and rest-based fMRI studies, evidence of disruptions has been found in the default mode, executive, and salience networks (Hamilton et al., 2013). The DMN has been one of the most extensively studied in MDD

as it contributes to essential processes including rest, cognition, and emotional processing which have been found to be altered in depression (Mulders et al., 2015).

1.2 The default mode network

The DMN is a system of brain regions whose functional activity is positively correlated during rest, and negatively correlated during attentionally demanding tasks. It has also been implicated in functional connectivity studies (McCormick et al., 2022). The significant regions used to characterize the network vary by studies, but the most statistically significant regions are the medial prefrontal cortex (MPFC), inferior/ lateral parietal lobes (LP), and the posterior cingulate cortex (PCC) or precuneus (Buckner et al., 2008). Many studies also include the medial temporal lobes (MTL), which encompass the hippocampus, as DMN functional connectivity exhibits network level alterations in the presence of MTL dysfunction. A study of interest is Henson et al. (2016) who explored 16 network connectivity in relation to the presence of hippocampal lesions in an amnesic patient. They found that at a network level, the hippocampal lesion was correlated with a significant reduction in patient functional connectivity across the DMN (Henson et al., 2016). The impact of which may not be limited to amnesic patients either. In depression, a 27-study review of resting-state functional connectivity by Kaiser et al. (2015) found consistent hyperconnectivity between the default network and the hippocampus. However, what we know about the DMN in the clinical population of patients with depression is limited in terms of methodology.

The origin of the functional contributions of the DMN was discovered in resting-state studies. Early DMN characterization found that the network of brain regions had a robust pattern of deactivation during task activity, otherwise recognized as the task negative network (Raichle, 2015). The observed reduction of activity during tasks and increased activity during a resting (default) state was central to how the term was coined (Raichle et al., 2001). The functional connectivity within the network throughout passive rest and some task states has also supported its involvement in cognitive processing (Greicius et al., 2003).

The DMN regions were found to be significantly active during tasks involved in internal thoughts, such as autobiographical memory, theory of mind, and future imaging (Buckner & DiNicola, 2019). A meta-analysis of 3 PET and fMRI studies explored regions which were significantly activated by autobiographical memory in contrast to a control word fluency task; specifically, these regions heavily overlapped with the default mode network including the hippocampal formation (Buckner et al., 2008). Further specialization of the network is evident in activation of the PCC during autobiographical memory and self-reference, MPFC in theory of mind and self-reference, and medial temporal lobe regions during episodic memory (Whitfield-Gabrieli & Ford, 2012). All of the behaviors described are those supported by the DMN and impacted in MDD.

1.2.1 DMN abnormalities in MDD

In the presence of depressive symptoms, word fluency has been behaviorally implicated, as reflected by the reduction in specificity on the autobiographical memory test and self-defining memory task. (Sumner et al., 2013). The correlation between behavior and neural signals has been instrumental in the definition of abnormalities. Differences in the DMN configuration in MDD have been found in resting-state studies using network-based independent component analysis (ICA) and region of interest seed-based correlations. In ICA studies, anterior regions of the DMN functionally connected to the MPFC have been found to be more synchronized irrespective of medication or course of the disorder while posterior regions connected to the PCC or precuneus show higher synchronization despite evidence of dissociation between the MPFC and PCC (Mulders et al., 2015). Seed-based analyses from the MPFC seed support the ICA results of increases in connectivity within the medial prefrontal, medial posterior, and lateral prefrontal regions (Mulders et al., 2015). The dissociation hypothesis is further supported as medication has been effective in the normalization of hyperconnectivity within the posterior regions (i.e., PCC) but has had limited improvements in the anterior regions (i.e., MPFC) (Li et al., 2013).

While studies of resting-state connectivity in patients have been instrumental in characterizing MDD abnormalities at a network level, this work does not directly address how they are related to cognitive processing. Investigation of network abnormalities

during engagement with naturalistic stimuli such as movies or auditory narratives, provides an opportunity to shed light on this relationship.

1.3 Naturalistic stimuli as a lens to brain and behavior

Although most of the functional work on the study of depression used resting-state MRI and PET, it does not mean that this line of work is without flaws. While resting-state work has been instrumental in the definition of functional topography, generalizability, and relations of network-level activity to behavior, some have argued that it is no better at characterizing brain behavior relationships compared to other imaging methods (McCormick et al., 2022). The use of resting-state in clinical fMRI investigations is further limited to correlations of state or trait level differences indirectly and is unable to characterize online processing during an active task state (Finn, 2021). Recently, the use of fMRI in combination with exposure to naturalistic stimuli has gained in popularity as it allows for the investigation of network engagement during controlled active cognitive states. Initial findings suggest it may also be more accurate in predicting trait cognition and emotion across individuals or clinical populations as compared to rest (Finn & Bandettini, 2021).

In a review by Lee and colleagues (2020), the authors highlighted the benefits of using narratives as naturalistic stimuli for understanding the role of the DMN in memory and cognition. The engagement or synchronization of the DMN is significant in both memory encoding and retrieval (Spreng et al., 2009). The increase of synchrony in DMN during encoding of a narrative is furthermore correlated with integration of information as it unfolds over time (Chen et al., 2016; Hasson et al., 2008). This pattern of DMN synchronization is different from rest as it is only present when participants encounter a stimulus that is narrative-like (Hasson et al., 2015; Lerner et al., 2011). As patients with MDD have impacts in both the brain regions related to the DMN and exhibit characteristic behavioral deficits in autobiographical memory that extend to the recall of narratives (Söderlund et al., 2014), the use of narrative stimuli in combination of fMRI can inform how DMN abnormalities relate to differences in cognitive processing.

1.3.1 Function of temporal hierarchy

The use of narratives to explore naturalistic language comprehension and the implicated information processing hierarchy originated in work conducted by Hasson et al. (2004). Using narratives as stimuli in combination with fMRI and with analyses of intersubject correlation demonstrated that, across individual participants, the free viewing of the same dynamic complex video is capable of inducing synchronization in both spatial and temporal patterns of the brain (Hasson et al., 2004). The synchronization is additionally impacted by the time scale of information integration that is required for narrative comprehension. Lerner et al. (2011) temporally decomposed a narrative into parts of paragraphs, sentences, and words to map the topographical regions involved in processing long to short timescale information, respectively. A minimum of sentence level information is required to reliably synchronize the DMN whereas the auditory cortex synchronized regardless of timescale differences (Lerner et al., 2011). With Nastase et al. (2021), the publication of large-scale datasets, which leveraged narrative stimuli, has highlighted the richness of resulting data and the value for examination of interindividual differences in network organization.

1.3.2 Prior studies in MDD

Some prior fMRI work on the involvement of DMN in processing naturalistic stimuli was conducted in the melancholic subtype of MDD and focused specifically on emotional processing. As participants viewed audiovisual movies which were negatively valanced and displayed inhuman treatment of prisoners, patients showed a decrease in the signal synchrony in the ventromedial prefrontal cortex, bilateral intraparietal sulcus, and right anterior insula, i.e., in regions thought to support emotional regulation or in this case reflected dysregulation (Guo et al., 2015). The functional connectivity of some of these regions in patients with melancholic MDD was additionally diminished compared to controls during the natural viewing process, with significant dysconnectivity in the bilateral superior temporal sulcus, STG, dorsal anterior insula, dorsal anterior cingulate cortex, and MPFC (Guo et al., 2016). The dorsal medial prefrontal cortex was particularly sensitive to differences in valance with significant dysconnectivity in positive compared to negative valence conditions (Guo et al., 2016). These findings suggest that

narrative processing is severely impacted by the presence of MDD. However, these studies are limited to emotional materials and the investigation of the melancholic subtype MDD. The processing of narratives without strong emotional content and any relationship to temporal information integration demands has not yet been addressed.

1.4 Current study

Based on the background reviewed, the goal of the present study was to examine the contributions of the DMN to narrative processing of naturalistic stimuli in patients with MDD. With this goal in mind, the research question we aimed to answer is how previously documented abnormalities in DMN in MDD relate to temporal integration demands during narrative processing. For this study, which was a part of a larger protocol, we recruited a sample of MDD patients with the treatment resistant variant and compared them with a group of matched control participants. Through the use of two experimental conditions, an Intact and Scrambled narrative, in combination with fMRI, we were able to manipulate the temporal integration demands and explore how patients with MDD synchronize brain activity while listening to naturalistic stimuli under low and high demand conditions. As patients with MDD exhibit many similarities in patterns of functional abnormalities to patients with amnestic mild cognitive impairments (Bai et al., 2012), whose temporal integration hierarchy is disrupted (Zuo et al., 2020), we specifically aimed to determine whether the involvement of regions of the DMN is altered during temporal integration of narratives in MDD. We hypothesized (1) that the involvement of DMN regions during narrative processing would be affected by MDD when comparing synchrony across participants; and (2) that abnormalities in the synchrony across DMN regions in MDD would be more pronounced for the Intact than Scrambled narrative condition.

Chapter 2

2 Methods

2.1 Participants

Twenty-two patients diagnosed with treatment resistant MDD and 20 controls participated in the study. Patients were clinically diagnosed with unipolar or bipolar MDD based on DSM-V criteria and failed at least one therapeutic treatment trial for MDD as documented by medical records. Some patients were previously diagnosed with comorbid disorders but were being treated for their diagnosis of MDD at the time of the study. The treating physician referred patients to the study prior to starting treatment at the Brain Stimulation Clinic at Parkwood Institute of St. Joseph Health Care in London, Ontario, Canada. Patients who had previously undergone ECT treatment within the past year were not eligible to participate. Control participants were recruited from Western University and from OurBrainsCAN registry in the greater London community. Recruitment was conducted after the enrollment of individual patients with an approximately yoked design to maximize demographic match based on gender, age, and education. All participants were between the ages of 18-85 without age related neurocognitive disorders, had basic English proficiency, and reported no major medical concerns that might interfere with cognitive testing or MRI. Control participants otherwise reported no diagnosed neurological, degenerative, personality, psychiatric or mood disorders, nor a history of substance abuse within the past 6 months. All participants provided written informed consent with procedures approved by the research ethics board at Western University and Lawson Health Research Institute.

2.2 Procedures

This project was part of a larger protocol on “Brain Mechanisms of Antidepressant Action in Electroconvulsive Therapy.” Only a subset of the study procedures and data is reported here. The current project focused on the comparison of MDD patients tested pre-stimulation treatment and controls in the fMRI component of the protocol that involved a narrative processing task. Additional clinical neuropsychological data are presented for characterization of general cognitive status in the patient sample.

2.2.1 Participant characteristics

All participants provided demographic information including age, gender, education, handedness, and medical history. Patients completed the Sheehan Disability Scale (SDS) as a measure of functional impairment (Sheehan et al., 1996). Patients and controls both completed the Patient Health Questionnaire (PHQ9) as a measure of potential depression (Kroenke et al., 2001). For one patient the PHQ-9 score was missing. Controls also completed the Depression Anxiety Stress Scales (DASS-42) as a measure of state depression, anxiety, and stress (Lovibond & Lovibond, 1995). Differences between groups where measures were available were estimated using a two-sample t-test. A summary table containing participant characteristics can be found in Table 1.

2.2.1.1 Neuropsychological measures

All participants completed a battery of tests which assessed core aspects of cognitive functioning including verbal learning, memory, attention, and verbal association. The Rey Auditory Verbal Learning Test (RAVLT) was administered to assess verbal learning and memory (Schmidt, 1996); Trail Making Test A & B (TMT) was administered to assess attention, speed, and mental flexibility (Adjutant General's Office, 1944); Symbol Digit Modalities Test (SDMT) was administered to assess attention, visual tracking, and motor speed (Smith, 1973); and FAS Word Fluency Test (FAS) was employed to probe verbal association fluency (Spreen, 1977). Each test score was z-normalized by age and education, if available (Smith, 1973; Strauss et al., 2006; Tombaugh, 2004). Differences between groups were estimated using a two-sample t-test. Effect size was estimated using Hedges' g correction. P-value and FDR corrected values were calculated. A summary table containing neuropsychological information can be found in Table 2.

Table 1. Summary of participant characteristics.

Scale	Patient	Control	T-score	P-value
Gender	13F/9M	11F/9M	-0.26	0.795
Age	39.55 (13.33)	37.8 (13.71)	-0.39	0.696
Years of Education	14.73 (2.49)	18 (2.64)	4.12	<.001***
Handedness	3L/19R	2L/18R	0.36	0.723
Comorbid disorders	PTSD = 1 Bipolar = 2 GAD = 3 Schizoaffective + Anxiety = 2	NA	NA	NA
SDS	25.59 (3.65)	NA	NA	NA
PHQ-9	18.43 (6.61)	2.8 (4.7)	-8.76	<.001***
DASS-42 Depression	NA	3.25 (6.75)	NA	NA
DASS-42 Anxiety	NA	3.15 (5.74)	NA	NA
DASS-42 Stress	NA	6.05 (7.87)	NA	NA

Note. Values are represented as means and standard deviations or ratios where applicable. *** represents a significant difference between groups at $p<.001$. PTSD = Post Traumatic Stress Disorder; GAD = Generalized Anxiety Disorder; SDS = Sheehan Disability Scale; PHQ9 = Patient Health Questionnaire; DASS-42 = Depression Anxiety Stress Scale.

Table 2. Summary of neuropsychological measures.

Test Name	Mean (SD) Patient	Mean (SD) Control	T-score	DF	Hedges g	P-value	p-FDR
RAVLT Total Immediate Recall	-0.51 (1.18)	0.89 (0.8)	-4.53	37.03	1.35	<.001***	<.001***
RAVLT Delayed Recall	-0.45 (1.17)	0.77 (0.67)	-4.18	33.87	1.24	<.001***	<.001***
TMT A	-0.99 (2.04)	0.14 (1.15)	-2.24	33.65	0.66	0.032*	0.032*
TMT B	-1.24 (1.8)	0.28 (1.28)	-3.17	37.91	0.95	0.003**	0.006**
SDMT (Written)	-0.48 (1.23)	0.81 (1.51)	-3.01	36.77	0.92	0.005**	0.006**
FAS	-0.64 (1.17)	0.33 (0.89)	-3.04	38.84	0.91	0.004**	0.006**

Note. Values are represented as z-score normalized means and standard deviations. Asterisks represents a significant difference between groups at *p<.05; **p<.01; ***p<.001. RAVLT = Rey's Auditory Verbal Learning Task; TMT = Trail Making Test; SDMT = Symbol Digit Modalities Test; FAS = Verbal Word Fluency.

2.3 Stimuli and experimental design

Stimuli for the experiment were generated from a 7.5-minute-long (450 seconds) narrative (‘Pie-man’) told by Jim O'Grady recorded at a live performance at The Moth in New York City (Lerner et al., 2011). The stimulus is a story that was presented auditorily using MRI-compatible earphones. The narrative is a dynamic story, which began with 13 seconds of neutral music, followed by 2 seconds of silence, and which was told from the first-person perspective of a journalist who navigated campus life through suspense and humor for a duration of 422 seconds. It ended with applause followed by 13 seconds of silence.

Each participant was presented with two conditions for the stimulus, an Intact and a Scrambled version, in that order. The Intact version of the stimulus is the story, unaltered in order, played from beginning to end, and contained a total of 957 words. The Scrambled version of the stimulus is the same story segmented word by word, and with a permuted order of these segments. Adjacent short words were combined into single segments in cases where they could not be separated, which resulted in a total of 608 words at an average duration of 0.7+/-0.5 seconds.

The experimental task differed in the demands for temporal integration, with the Intact story requiring integration of information across longer periods of time. The accumulation and integration of temporal information over many minutes has reliably synchronized higher-order brain regions including the temporal parietal junction, angular gyrus, PCC, MPFC, and hippocampus in prior research (Ben-Yakov et al., 2012a, p.; Chen et al., 2016; Simony et al., 2016). Meanwhile, the Scrambled story typically only leads to synchronization in the sensory areas, such as A1+, but not in higher-order association regions (Lerner et al., 2011).

2.3.1 Behavioral test

To assess whether participants attended to and comprehended the experimental stimuli in the Intact condition, a 24-item questionnaire with 3 alternative forced choice format was presented at the end of the scan session, outside of the scanner (see Appendix A). Participants were asked to identify accurate details of the experimental stimulus they had

heard, and they were encouraged to guess if they were unsure of the answer. The questions probed content at timepoints throughout the Intact narrative after a short delay. The questions additionally varied in integration demands, such that the answer could only be derived if the participant successfully integrated the information across 1 sentence, 2 sentences, 3 sentences, or 4 sentences.

2.4 Image acquisition

Images were acquired on a 3 Tesla MR scanner (Prisma; Siemens) using a 32-channel head coil. Before the fMRI sequences, a whole head structural T1-weighted magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) volume (TE = 2.28 ms, TR = 2400 ms, TI = 1060 ms, resolution = 0.8 X 0.8 X 0.8 X 0.8 mm isometric) was acquired. Two fMRI whole brain sequences (runs) were acquired, one for each experimental condition, Intact condition followed by Scrambled condition. Each acquisition included 310 volumes and consisted of 68 T2*-weighted echo planar imaging (EPI) pulse sequence slices with an in-plane resolution of 2.0 X 2.0 mm (TE = 39 ms, TR = 1500 ms, flip angle = 50-degree, slice thickness = 2.0 mm, FOV = 220 mm, parallel imaging with grappa factor = 2). The slices were acquired in an odd-even interleaved fashion in the anterior to posterior direction.

2.5 Preprocessing

MRI data were converted to brain imaging data structure (BIDS) format and run through fmriprep-v20.2.1 (Esteban et al., 2019). This preprocessing included: motion correction, slice time correction, susceptibility distortion correction, registration from EPI to T1w image, confounds estimation, (e.g., 6 parameter motion, white matter [WM], and cerebrospinal fluid [CSF]), normalization to standard MNI152 non-linear 6^{th} generation asymmetric (MNI152NLin6Asym) template space, and resampling to 2 mm isovoxel (see Appendix B). The functional images were preprocessed using denoise-fmri (https://github.com/akhanf/denoise-fmri) level 1 rule to regress out basic confounds which included head motion, WM, and CSF calculated in fMRIPrep (Satterthwaite et al., 2013). Head motion was estimated through rigid-body 6 parameters of motion (x- y- z- translation and rotation) and corrected. WM and CSF are considered spatial non-neuronal

sources of signals that reflect physiological and hardware noise unrelated to brain networks and filtered out (Whitfield-Gabrieli & Nieto-Castanon, 2012). Global signal tends to be included in basic confounds, however recent studies suggest that global signal regression may regress out related network sources from the DMN and thereby are excluded due to our focus on DMN sources (Scalabrini et al., 2020).

Preprocessing of the functional data did not include any spatial smoothing for two reasons. The method of ROI-based intersubject correlation averages the signal across all voxels within each ROI, with spatial smoothing having limited impact. Smoothing, while it will increase the similarity of our neighboring voxels, will include the influence of activity in the voxels outside of the ROI or decrease spatial specificity (Nastase et al., 2021).

2.6 Regions of Interest (ROI)

Regions of interest were selected based on a priori hypotheses regarding the brain regions impacted by MDD. We were particularly interested in the DMN as there are widespread impacts in the network which includes the hippocampus and all regions have been previously found to be significantly correlated in temporal processing (Ben-Yakov et al., 2012b; Lerner et al., 2011). A1+ auditory cortex is a region of the brain functionally defined from the ISC of the reverse 'Pie-man' condition from an independent control sample (Lerner et al., 2011). The A1+ region reliably responds to the presence of auditory stimuli irrespective of temporal integration manipulations and acts as a control region that should be synchronized in both experimental conditions (Lerner et al., 2011). The DMN ROIs were extracted from an atlas defined by a resting-state connectivity analysis (http://findlab.stanford.edu/functional_ROIs.html) which could be mapped with largely similar results as a continuous narrative (Chen et al., 2017; Simony et al., 2016). The DMN regions selected were the posterior medial cluster (PMC), the medial prefrontal cluster (PMC) and the lateral parietal cluster, specifically angular gyrus (Shirer et al., 2012). The latter region was extracted separately in the left (LPL) and right (LPR) hemisphere. Independent left (HippL) and right hippocampus (HippR) were extracted from the structurally defined HippUnfold atlas (DeKraker et al., 2022) and examined to explore potential lateralized effects of the hippocampus. All ROIs were extracted from

normalized MNI152NLin6Asym template space, and if necessary, resampled to 2 mm isovoxel (Figure 1).

Figure 1. Regions of interest in MNI152 non-linear 6th generation asymmetric template space

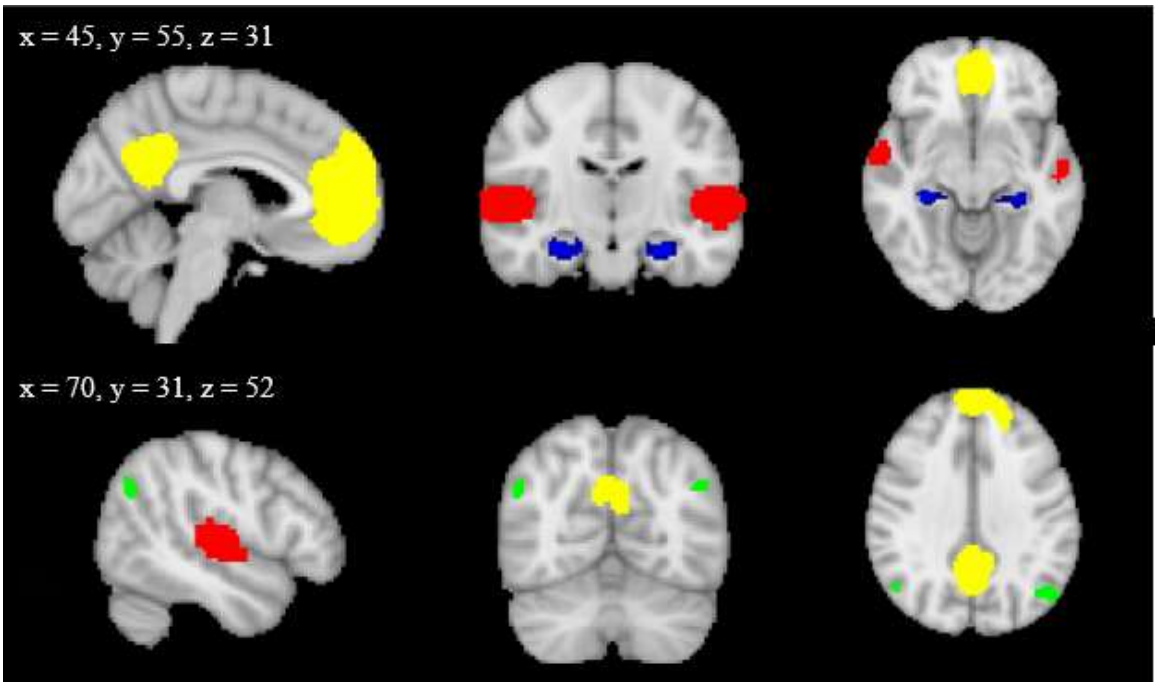


Figure 1. A1+ bilateral auditory cortex = red, medial prefrontal and posterior medial clusters (independent) = yellow, lateral hippocampus (independent) = blue, lateral angular gyrus (independent) = green.

2.7 Intersubject correlation (ISC)

Functional activity was analyzed using the intersubject correlation (ISC) approach, measuring the similarity of neural responses across time between individuals who were presented with the same stimuli (Hasson et al., 2004; Lerner et al., 2011; Nastase et al., 2019). The ISC analysis was run using a custom MATLAB 2020b script. For each ROI, the BOLD signal was extracted for each participant as an average normalized z-score for each TR to plot the ROI signal over time (i.e., over the sequence of # functional volumes acquired). The intersubject correlation was then calculated with a leave-one-out approach as the Pearson product-moment correlations between that ROI's BOLD time course in one individual to the average of that ROI's BOLD time courses in the remaining individuals in the group (Lerner et al., 2018). We compared patients to controls using the correlations of each patient with MDD to the mean of the controls.

2.7.1 Replication analysis in controls

To confirm that fMRI data in our control sample are comparable to those reported in previous literature, an examination of the control group variation of both experimental conditions was conducted. In this within-group analysis, we used Pearson correlation to measure the statistical association between the response time course for each control participant and other participants of the control group (n-1) at each ROI, and tested this coefficient against a value of 0, using a one sample t-test. The coefficient was also tested between conditions to determine whether DMN ROIs were significantly more synchronized in the Intact compared to Scrambled condition, or significantly involved in temporal integration of long-time scale information, as shown in prior work (Lerner et al., 2018).

2.7.2 Group analysis

To test for differences between groups, each participant's (patient or control) time courses, separated by each ROI and experimental condition, were correlated with the mean time course observed in the control group (with leave-one-out constraints for controls). The Pearson correlation values for individuals in both groups were then examined with a two-by-two mixed ANOVA for each ROI to determine within-subjects

condition effects (Intact vs. Scrambled) and between-subjects group effects (Patients vs. Controls). A two-tailed t-test with Bonferroni correction for the number of conditions were performed for further exploration of significant interactions.

Chapter 3

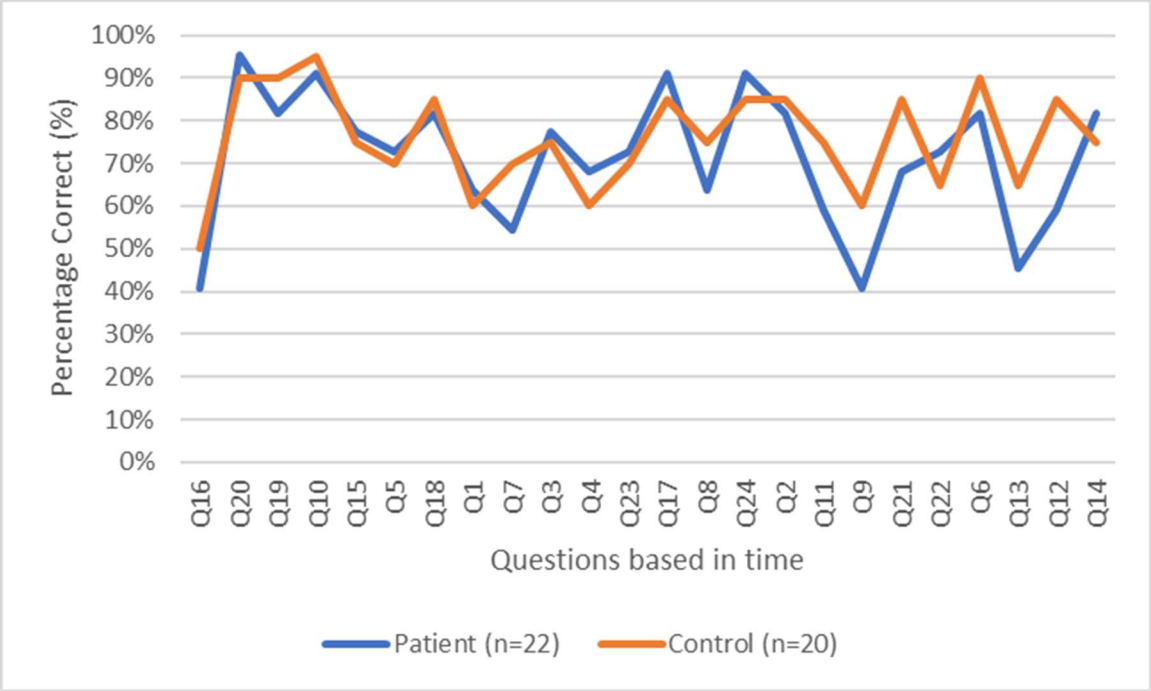
3 Results

3.1 Behavioral test

On average, both groups of participants were able to correctly identify a similar number of answers from the behavioral test, at 75.8% and 71.4% for controls and patients, respectively. A Welch Two Sample t-test found that the overall performance across items was not significantly different across groups ($t[1004.28] = 1.6$, $p = 0.111$, see Figure 2A. When the questions were binned (n = 8) by the number of sentences that had to be integrated across the narrative (short = 1, medium = 2, long = 3 or 4) to derive the correct answer, a mixed effects ANOVA found that there was no main effect of group ($F[1, 1002] = 2.53$, $p = 0.112$, there was no main effect of integration demands ($F[2, 1002] = 0.05$, $p = 0.947$), and there was no interaction ($F[2, 1002] = 0.89$, $p = 0.41$), see Figure 2B.

Figure 2. Behavioral performance in an immediate recognition task.

A. Average group performance over time



B. Average group performance by integration demands

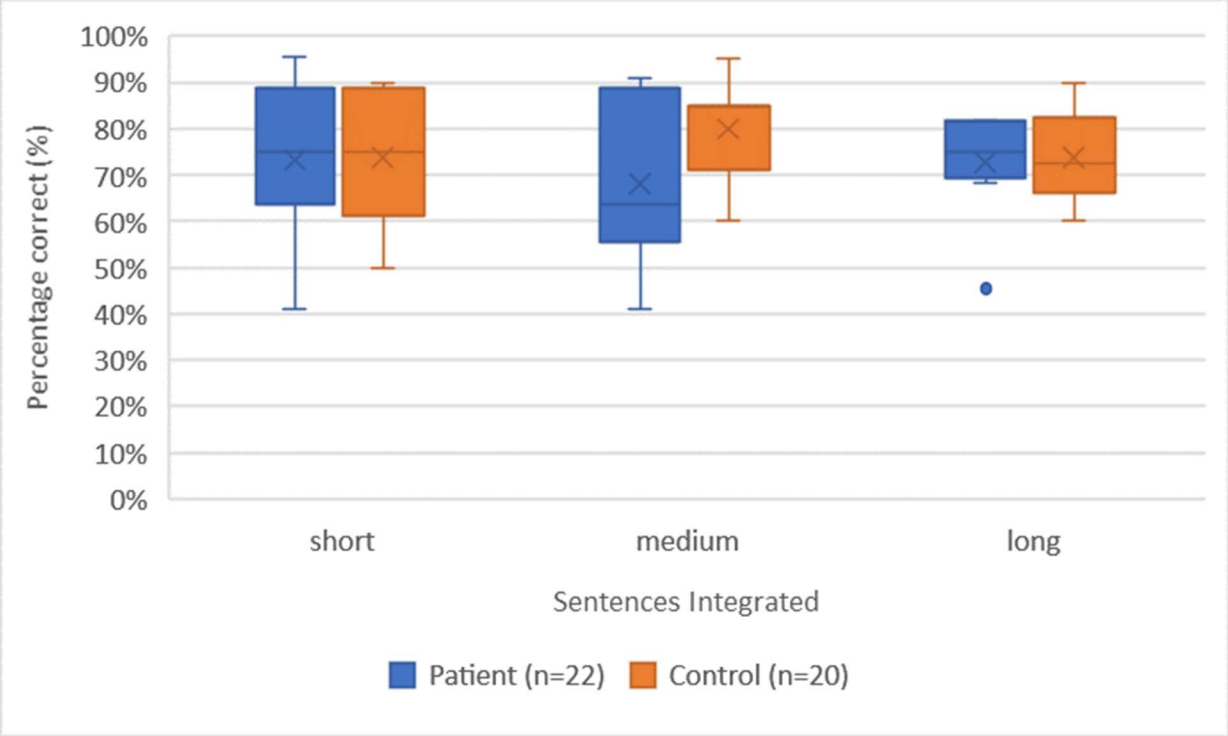


Figure 2. A. Average performance on questions from the behavioral test, ordered by the timepoint of the narrative that the question probed (i.e., Q16 probed an early statement in the narrative). Individual points represent the average performance of the group per question. B. Box and whisker plots for behavioral test with questions binned by integration demands. A total of 8 items contributed to each bin. X represents the mean, midline represents the median, box represents the interquartile range, whiskers represent minimum and maximum excluding outliers and points outside the whiskers are outliers. Short = integration over 1 sentence in the narrative, Medium = 2 sentences, Long = 3 to 4 sentences.

3.2 Intersubject correlations

3.2.1 Replication analysis in controls

The within-group ISC for the control group for each ROI is plotted in Figure 3. To determine if the intersubject correlation was significantly correlated, or non-0, a one-sample t-test was performed for each ROI for each condition. To determine if the intersubject correlation was significantly different between the conditions, a paired samples t-test was performed for each ROI.

In the Intact condition, the following ROIs were significantly non-0: A1+ ($t[19] = 19.09$, $p < 0.001$), PMC ($t[19] = 6.45$, $p < 0.001$), HippR ($t[19] = 3.86$, $p = 0.001$), MPFC ($t[19] = 5.07$, $p < 0.001$), LPL ($t[19] = 3.28$, $p = 0.004$), and LPR ($t[19] = 3.4$, $p = 0.003$). HippL ($t[19] = 2.04$, $p = 0.055$) was the only ROI in which activity was not significantly synchronized across participants.

In the Scrambled condition, the only ROI which was significantly non-0 was A1+ ($t[19] = 20.01$, $p < 0.001$). All other ROIs were not significantly synchronized: PMC ($t[19] = 2.06$, $p = 0.053$), HippL ($t[19] = 0.81$, $p = 0.427$), HippR ($t[19] = -1.73$, $p = 0.1$), MPFC ($t[19] = 0.99$, $p = 0.333$), LPL ($t[19] = -1.46$, $p = 0.16$), and LPR ($t[19] = 2.04$, $p = 0.055$).

Between the conditions, the following ROIs showed a significant difference, specifically a reduction in their ISC for the Scrambled condition as compared to the Intact condition: PMC ($t[19] = 5.04$, $p < 0.001$), HippR ($t[19] = 4.25$, $p < 0.001$), MPFC ($t[19] = 3.88$, $p = 0.001$), LPL ($t[19] = 3.65$, $p = 0.002$), and LPR ($t[19] = 2.21$, $p = 0.039$). The following ROIs did not show a significant difference between changes in condition: A1+ ($t[19] = -1.1$, $p = 0.286$), and HippL ($t[19] = 1.08$, $p = 0.293$). The reduction in these ROIs between conditions generally replicated the reduction of DMN synchronization reported in previous studies (Lerner et al., 2011).

Figure 3. Intersubject correlations of fMRI signals in control participants.

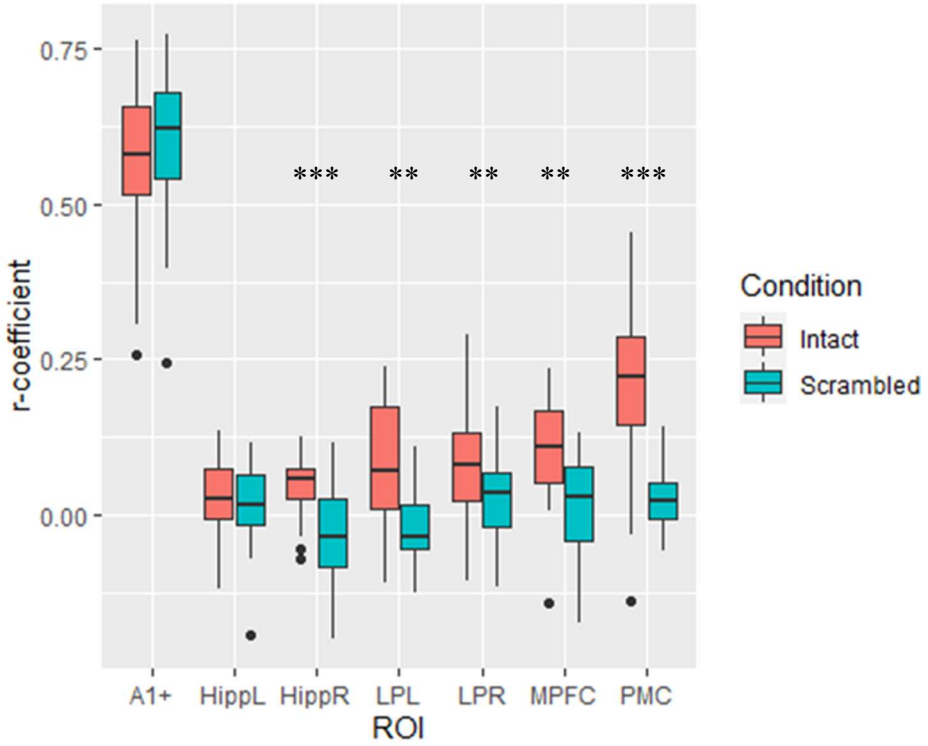


Figure 3. Intersubject correlation of controls, n = 20, showed the temporal disruption between conditions in our a priori ROIs where DMN regions are only significantly correlated during the Intact condition. Midline represents the median, box represents the interquartile range, whiskers represent minimum and maximum excluding outliers and points outside the whiskers represent outliers. Asterisks represents a significant difference between conditions at $^{**}p<.01$; $^{***}p<.001$. A1+ = auditory cortex; HippL = left hippocampus; HippR = right hippocampus; LPL = left lateral angular gyrus; LPR = right lateral angular gyrus; MPFC = medial prefrontal cluster; PMC = medial posterior cluster.

3.2.2 Group Analysis

The between-group ISC for each ROI is plotted in Figure 4. A two-by-two mixed effects factorial ANOVA was run for between-subjects group (control vs. patient) and within-subjects condition (Intact vs. Scrambled story) for each region of interest.

The only ROI which showed a main effect of group was the LPL ($F[1, 40] = 9.78$, $p = 0.003$). All other ROIs were not significant: A1+ ($F[1, 40] = 0.79$, $p = 0.38$), PMC ($F[1, 40] = 0.42$, $p = 0.522$), HippL ($F[1, 40] = 0.03$, $p = 0.875$), HippR ($F[1, 40] = 1.9$, $p = 0.176$), MPFC ($F[1, 40] = 1.54$, $p = 0.222$), , and LPR ($F[1, 40] = 1.07$, $p = 0.307$).

All DMN regions showed a significant main effect across conditions: PMC ($F[1, 40] = 52.28$, $p < 0.001$), HippL ($F[1, 40] = 8.27$, $p = 0.006$), HippR ($F[1, 40] = 14.4$, $p < 0.001$), MPFC ($F[1, 40] = 54.62$, $p < 0.001$), LPL ($F[1, 40] = 25.78$, $p < 0.001$), and LPR ($F[1, 40] = 27.63$, $p < 0.001$). The only ROI which did not have a main effect across condition was the A1+ ($F[1, 40] = 3.69$, $p = 0.062$).

An interaction effect was observed in the HippR ($F[1, 40] = 7.26$, $p = 0.01$), and MPFC ($F[1, 40] = 4.62$, $p = 0.038$). In all other ROIs this effect was not significant: A1+ ($F[1, 40] = 0.05$, $p = 0.829$), PMC ($F[1, 40] = 0.3$, $p = 0.587$), HippL ($[1, 40]F = 2.01$, $p = 0.164$), LPL ($F[1, 40] = 0.08$, $p = 0.777$), and LPR ($F[1, 40] = 3.25$, $p = 0.079$). In order to help interpret the pattern of results reflected in the significant interaction term, we examined group effects separately for each experimental condition. In the right hippocampus, patients ($\bar{x} = 0.02$, SD = 0.06) were found to show a significantly higher ISC compared to controls ($\bar{x} = -0.03$, SD = 0.08) only in the scrambled condition ($p = 0.019$, Bonferroni corrected; for Intact Condition $p = 0.453$). In the medial prefrontal cortex, patients ($\bar{x} = 0.16$, SD = 0.08) exhibited a significantly higher ISC compared to controls ($\bar{x} = 0.1$, SD = 0.09) only in the Intact condition ($p = 0.032$, Bonferroni corrected; for Scrambled condition $p = 0.741$).

Figure 4. Intersubject correlations of fMRI signal in MDD patients versus control participants.

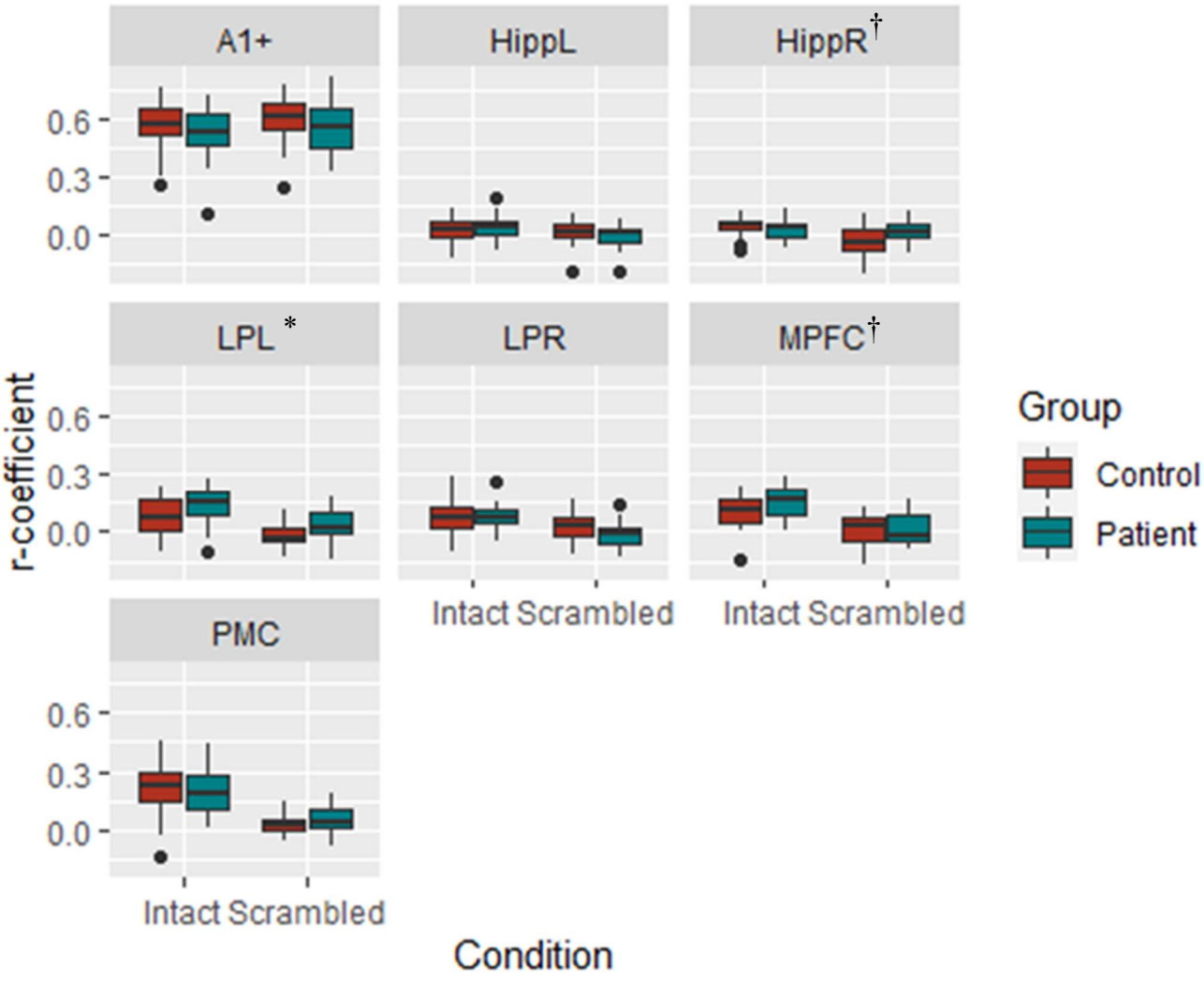


Figure 4. Intersubject correlation of controls (n = 20) compared to patients (n = 22) showed the temporal pattern between conditions and group in our a priori ROIs. The r-coefficient ISC values of the control group are the same as those presented in Figure 3. Midline represents the median, box represents the interquartile range, whiskers represent minimum and maximum excluding outliers and points outside the whiskers represent outliers. Asterisks represents a significant main effect of group at *p<.05. Daggers represent a significant interaction effect at †p<.05. A1+ = auditory cortex; HippL = left hippocampus; HippR = right hippocampus; LPL = left lateral angular gyrus; LPR = right lateral angular gyrus; MPFC = medial prefrontal cluster; PMC = medial posterior cluster.

Chapter 4

4 Discussion

We set out to examine how the process of temporal integration in an auditory narrative is impacted by MDD in DMN regions, a question which has not been previously explored in this population. We were able to replicate previous findings that the DMN is involved in the temporal integration during narrative processing in our control sample. We were also able to extend this finding to MDD patients, such that the DMN was only significantly more synchronized during an Intact than a Scrambled narrative. We were also able to extend the findings in our reliability analysis by using independent hippocampus ROIs showing that only the right hippocampus is significantly synchronized in the processing of an Intact narrative. Additionally, we found significant differences in the synchronization of MDD patients, with the left angular gyrus being more synchronized across both conditions, the MPFC being more synchronized in the Intact condition, and the HippR being more synchronized in the Scrambled condition compared to controls. The results, however, were not in the direction that we expected, with observed increases rather than decreases in synchrony in ROIs for MDD patients. While patients demonstrated a difference in the synchronization of the brain during narrative integration, their behavioral performance to maintain and recall the information from the Intact narrative in a short-delay task appeared to be well preserved. Meanwhile, patients exhibited characteristic deficiencies of performance across all neuropsychological tests that were administered. Overall, we were able to demonstrate that patients with MDD have a different signature of brain synchronization during the processing of narrative integration in regions previously implicated in the disorder.

4.1 Relationship to findings in resting-state

Compared to resting-state, it is evident that the application of a narrative paradigm is effective for the characterization of functional differences in the DMN across experimental conditions, and can also be used to reveal abnormalities in patients with MDD. Our study extends previously reported functional differences in the DMN in MDD as the use of intersubject correlation allowed us to probe the specific process of narrative

integration in an experimental controlled manner for naturalistic stimuli, a process that cannot be probed in resting-state (Finn, 2021). It is clear from our neuropsychological measures that patients had significantly decreased performance across measures of executive functioning on the RAVLT, TMT, SDMT, and FAS, which is in line with previous studies of depression (Burt et al., 1995; Söderlund et al., 2014). Results from our behavioral questionnaire did not suggest that the overall behavior resulting from temporal integration was severely impacted, but the functional differences observed during scanning suggest that patients are engaged with the narrative differently to encode the information. It is important to note that our behavioral questionnaire was not specifically designed to probe memory operations or hippocampally dependent context processing. Instead, it probed a combination of memory and attention similar to a post-scan behavioral validation (Chen et al., 2016; Simony et al., 2016). However, compared to trait description and correlations of MDD behaviors with resting-state abnormalities, we arguably present a more direct manner of assessing how information is integrated and maintained differently in this clinical condition.

4.2 Temporal hierarchy of narrative processing in MDD

The DMN results here replicated its involvement in the temporal hierarchy of narrative integration but extend the literature that the hippocampus may not be bilaterally synchronized (Chen et al., 2016, 2017; Lerner et al., 2011). Some disruptions of DMN engagement through the manipulation of temporal integration demands (through scrambling) (Hasson et al., 2008; Lerner et al., 2011, 2018), are furthermore retained in patients with MDD, which has not been shown previously. We were also able to extend the literature on the temporal hierarchy of regional cortical involvement in narrative processing to MDD by showing differences in the MPFC that were specific to the Intact condition that required integration. The main effect of group in the LPL suggests a greater consistency of left lateralized processing in the angular gyrus, which is significantly more synchronized in patients than controls. However, it does not appear that the abnormalities of the group are related to temporal integration demands as the effect is maintained despite condition in the LPL being significantly more similar rather

than different to controls, a finding that was not expected. Our results converged with those reported in adolescents by Gruskin et al. (2020), which showed that participants with similar levels of depressive symptom severity have a more similar BOLD activity in the left angular gyrus and right precuneus. This could have also driven our increased synchrony as our sample may be more homogenous due to the treatment-resistant nature of their diagnosis. However, our results diverge from other studies that found a reduction in both the synchronization and degree centrality in many regions in the presence of MDD in processing of emotional materials (Gruskin et al., 2020; Guo et al., 2015, 2016). It has also been suggested that the DMN is modulated by attention particularly in the MPFC (Chen et al., 2016; Cohen & Parra, 2016; Ki et al., 2016; Schmälzle et al., 2015). However, the inferential nature of what drives the changes in the ISC cannot be made as ISC can only be used to describe the consistency of the brain signal to the stimuli but not the cause (Nastase et al., 2019). The interaction effect of the HippR also supports the lateralized processing of low-level temporal information (words), which could suggest differential engagement in MDD. Despite the difference between groups, the synchronization of the ROI is not significant during the Scrambled condition in patients, thus we refrain from suggesting that the differences relate to abnormalities in MDD.

4.3 Hyperconnectivity in MDD

Irrespective of the casual limitations, what we can conclude from ISC is that the regions of brain are involved in the processing of the stimuli, or that the regions are consistently engaged when listening to the narrative. Overall, the observed differences in intersubject correlation appear in line with the network hyperconnectivity hypothesis that the default mode network is more consistently and functionally involved in the presence of depression (Li et al., 2013; Mulders et al., 2015), rather than the network dissociation hypothesis that the network is disorganized (Mulders et al., 2016), which we initially hypothesized. The hyperconnectivity hypothesis posited that the DMN increase in connectivity during resting-state is a hallmark of MDD as it has been correlated with various behaviors (Z. Zhu et al., 2022). The middle temporal gyrus and the MPFC, which are characterized by hyperconnectivity between regions in MDD (Kaiser et al., 2015), have been inversely correlated with symptom severity suggesting that the neural changes

could be adaptive to cope with depression (R. Zhang et al., 2020; Z. Zhu et al., 2022). Our results suggest that this change is related to differences in narrative processing as the regions of the DMN are more consistently engaged in MDD under experimentally controlled conditions. Treatment effects of normalization in the abnormally elevated functional connectivity in the DMN further support that hyperconnectivity in MDD requires management for effective outcomes (Liston et al., 2014).

4.4 Limitations

First, in MDD, there is a high rate of comorbidity with other mood disorders (Avenevoli et al., 2015), which makes the disorder difficult to characterize as an independent entity. However, as MDD does not occur independently but co-occurs with other disorders, our sample could be more generalizable as it has been suggested that comorbidities should be treated together as they confound the evaluation and management of depression (Berlim & Turecki, 2007). Our clinical sample additionally differs as all patients were referred to ECT treatment after failing to show significant improvements after one or more pharmacological treatments, otherwise known as treatment-resistant depression. While our patient sample may not be completely homogenous in terms of a pure MDD diagnosis, we are confident that our sample is characteristic of this form of pre-treatment MDD patients.

As with other studies that employ ISC, we did not directly compare the individual response to specific aspects of the stimuli other than temporal integration demands. Instead, our analysis focused on the consistency of the response over time across the sample, so we infer that significantly synchronized regions encode information about the stimulus is consistent across individuals. As intersubject correlation is limited to modelling individual response to the experimental stimuli or variability, results may differ based on differences in samples and stimuli which is presented. Our sample was relatively small which additionally limits our ability to generalize our results. Larger analyses of within and between samples would be required to determine if the differences observed are consistent over the course of the disease, using different narratives, and across samples of different individuals.

4.5 Future directions

Future studies can more directly investigate the pattern of responses in MDD within patients over repeated presentations or presentations of different narratives to study if increased synchronization in the DMN is maintained in the brain regions presented here. Our analyses could also be extended to other regions of the brain as those presented here were determined based on a priori hypotheses. Future analyses of the data could explore the hippocampus in finer detail including consideration of contributions of different subfields or segmentation along the anterior and posterior axis. The hippocampus has been found to be differentially engaged as evident in the difference in temporal autocorrelation where single voxels change slowly or quickly over time along the medial-lateral gradient (Bouffard et al., 2022; Brunec et al., 2018). This type of differential engagement pattern can go undetected as our current model relied on time courses averaged across the entire ROI (Zuo et al., 2020).

The ISC observed in our study could also be compared with those observed in other samples that used the 'Pie-man' narrative to explore consistency within the larger population of individuals without MDD. Nastase et al. (2021) previously published data in a total of 82 healthy participants in BIDS format who listened to the 'Pie-man' narrative. This large dataset allows researchers to compare data and validate our ROI effects, as well as comparisons with MDD since intersubject correlation results are known to be sensitive to variation across samples. An extension of the ISC analysis is to explore temporal and spatial patterns (Nastase et al., 2019). Temporal intersubject functional correlation can be used to compute the correlation between the activity of multiple brain regions (Simony et al., 2016) to explore how regions fluctuate together. Spatial intersubject correlation can compute the correlation between spatially distributed responses (Chen et al., 2017) to search for events which increase or decrease synchrony of signal response. The two methods can also be combined to measure the consistency of spatiotemporal response patterns (Feilong et al., 2018).

There is optimism that as we continue to study ISC in clinical populations. As such there is room for greater adoption of functional techniques as they enable observation of functional responses during behavioral processing. While resting-state fMRI

investigation is a widely used methodology in both basic research and in clinical applications, we have shown here that a narrative paradigm can be used to characterize functional abnormalities in processing naturalistic stimuli in patients with MDD. Previous studies have found that even in disorders of consciousness (Iotzov et al., 2017) it is possible to engage participants and observe higher-order processing with exposure to complex naturalistic stimuli. The functional differences in processing narratives not only show how the brain translates information into behavior, but what brain region is disrupted. Significant regions of differences could be used to inform focal treatments which target specific regions of the brain. In a disorder like MDD, which can result from varied brain abnormalities that present as different symptoms, synchrony differences provide objective online measures of functional abnormality.

4.6 Conclusions

We explored the use of naturalistic functional neuroimaging to examine potential effects of disruption in the narrative processing of patients with MDD. By using ISC to assess synchrony of ROIs, which is typically disrupted in MDD in the resting-state, we were able to determine which regions in the DMN showed a similar or different engagement as controls. Our results support the idea that DMN regions are functionally involved in the processing of information which spans over long timescales. As compared to controls, MDD patients displayed a greater consistency of the left angular gyrus response with significantly higher synchronization than controls. The synchronization in the medial prefrontal cortex is also significantly greater in patients and can be linked specifically to processes of temporal integration. Taken as a whole, these findings suggest that patients with MDD modulate brain activity differently during narrative processing compared to controls. This is an important relationship which deserves further exploration in future studies focusing on relationships to behavioral effects, clinical symptoms, and potential impact of treatment.

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Appendices

Appendix A. Pie Man Comprehension Questionnaire

Instructions: For each question, select the statement (a, b, or c) that best answers the question.

1. What was the first thing the narrator did to make his story better?
    a. He gave Pie Man a name
    b. He made Pie Man an avenger
    c. He described Pie Man's ambition

2. What does the Latin sentence that Pie Man shouted mean in English?
    a. Listen to the voice of the people
    b. Knowledge is power
    c. I am not an animal

3. What was the newspaper editor's reaction to the narrator's completed Pie Man story?
    a. He was hesitant about publishing it
    b. He wanted the narrator to add more drama to it
    c. He loved it and wanted it on the front page

4. Why did the Pie Man contact the narrator?
    a. To notify him of the attack
    b. To complain about the lies in the story
    c. To ask him to invite more people to witness the attack

5. What was the newspaper editor's reaction when the narrator first told him about the attack on Dean McCowen?
    a. He thought the story was too dramatic
    b. He wanted the narrator to give the attacker a name
    c. He wanted the narrator to write a story about it because he did not like the dean

6. Why did the Ram run five stories about Pie Man?
    a. He was a sensation
    b. There was nothing else to publish
    c. The narrator was friends with Pie Man

7. What description is NOT true about the Pie Man in the news story?
    a. He clicked his heels as he fled the attack scene
    b. He reprimanded his victims for what they did
    c. He was wearing a mask

8. Where did Pie Man emerge from when he attacked Sheila?

a. The main entrance of the library
b. From behind a library drop box
c. The side entrance of the student dorm

9. When did Pie Man start wearing a cape?
    a. After the first story had been published
    b. When he made his first attack
    c. He never wore a cape

10. What did the Pie Man do?
    a. He offered Dean McCowen a cream pie
    b. He mashed a cream pie into Dean McCowen's face
    c. He mashed a cream pie into his own face in front of Dean McCowen

11. Why is it funny when the narrator asks the listeners NOT to spread the rumor about Sheila?
    a. Sheila is sitting in the audience
    b. He just spread it himself
    c. The rumor is not true

12. Why did Angela talk to the narrator?
    a. To ask about Pie Man
    b. To give him some leads on a potential news story
    c. To get in touch with Pie Man

13. How does the narrator typically interact with Angela?
    a. He has been openly flirting with her
    b. He has been subtly flirting with her
    c. He has been flirting with her friend to get her attention

14. How did the narrator justify saying that he was Pie Man?
    a. He became good friends with Pie Man and knew he wouldn't mind if the narrator pretended to be him
    b. He brought Pie Man into being and popularized him
    c. Pie Man asked the narrator to protect him against potential revenge by pretending to be Pie Man

15. What was Dean McCowen's reaction when the narrator asked him to comment on Pie Man's attack?
    a. He commented on students' increasing misbehaviors
    b. He said he wanted to investigate the case
    c. He cursed the narrator

16. Where, geographically in the United States, did the narrator begin his illustrious journalism career?
    a. The Bronx

b. Brooklyn
c. Manhattan

17. Why was Sheila the victim of an attack?
    a. She helped raise the tuition fee
    b. She helped ban outdoor drinking on campus
    c. She lacked school spirit

18. How did the narrator "cross the line" in his reporting of the Pie Man story?
    a. He made things up
    b. He had personal interaction with his sources
    c. He expressed biased opinions

19. What was the narrator doing when he first saw Pie Man?
    a. He was interviewing a student about the tuition raise
    b. He was interviewing Dean McCowen about the tuition raise
    c. He was walking past Dean McCowen

20. What was the name of the school newspaper?
    a. The Herald
    b. The Ram
    c. The Reflector

21. How did the real-life Pie Man change after the first story was published?
    a. He changed his outfit and actions to match the description in the story
    b. He started to go after more obvious targets
    c. He started to linger around after the attacks so that people could see him better

22. How was the Pie Man story received by the school?
    a. The dean wanted to censor it
    b. Students were skeptical about it
    c. People started to dress like him

23. How did the narrator describe Sheila as being different from all the other Fordham students?
    a. She is well-bred
    b. She works multiple part-time jobs
    c. She has outstanding grades

24. What was Sheila's reaction to the attack?
    a. She yelled at Pie Man
    b. She ran to Dean McCowen's office to report the attack
    c. We don't know; the narrator did not tell us

Appendix B. fMRIPrep Citation

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 20.2.1 (@fmriprep1; @fmriprep2; RRID:SCR_016216), which is based on *Nipype* 1.5.1 (@nipype1; @nipype2; RRID:SCR_002502).

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` [@n4], distributed with ANTs 2.3.3 [@ants, 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, @fsl_fast]. Brain surfaces were reconstructed using `recon-all` [FreeSurfer 6.0.1, RRID:SCR_001847, @fs_reconall], and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle [RRID:SCR_002438, @mindboggle]. Volume-based spatial normalization to two standard spaces (MNI152NLin6Asym, 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 templates were selected for spatial normalization: *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* [@mni152nlin6asym, RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym], *ICBM 152 Nonlinear Asymmetrical template version 2009c* [@mni152nlin2009casym, RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym],

Functional data preprocessing: For each of the 3 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Susceptibility distortion correction (SDC) was omitted. The BOLD

reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration [@bbr]. Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` [FSL 5.0.9, @mcflirt]. BOLD runs were slice-time corrected using `3dTshift` from AFNI 20160207 [@afni, RRID:SCR_005927]. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion. 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 MNI152NLin6Asym 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 Power (absolute sum of relative motions, @power_fd_dvars) and Jenkinson (relative root mean square displacement between affines, @mcflirt). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* [following the definitions by @power_fd_dvars]. The three global signals are 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*, @compcor]. Principal components are 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) are 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 is obtained by dilating a GM mask extracted from the

FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are 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 [@confounds_satterthwaite_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]. Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 [@nilearn, RRID:SCR_001362], mostly within the functional processing workflow. For more details of the pipeline, see [the section corresponding to workflows in *fMRIPrep*'s documentation](https://fmriprep.readthedocs.io/en/latest/workflows.html "FMRIPrep's documentation").

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