Stability of Networks in Young Adults in Remission from Major Depressive Disorder

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THESIS

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LIST OF ABBREVIATIONS

aFTN	anterior Frontotemporal Network
CCN	Cognitive Control Network
cDMN	core Default Mode Network
dFPN	dorsal Frontoparietal Network
DMN	Default Mode Network
fc-rsMRI	Functional Connectivity of Resting-State Magnetic Resonance Imaging
HCs	Healthy Controls
ICC	Intraclass Correlation Coefficient
lFPN	lateral Frontoparietal Network
HDRS	Hamilton Depression Rating Scale
LME	Linear Mixed Effects
MDD	Major Depressive Disorder
rMDD	remitted Major Depressive Disorder
vDMN	ventral Default Mode Network

SUMMARY

Although neurobiological research has pushed for determining biomarkers of major depressive disorder (MDD), the test-retest reliability of functional connectivity resting-state magnetic resonance imaging (fc-rsMRI) has not been assessed. Individuals with MDD and those in remission from MDD typically show increased fc-rsMRI within the default mode network (DMN), characterized as a set of regions coordinated in activity during mind-wandering or rest. Evidence in MDD also suggests aberrant connectivity between the DMN and cognitive control network (CCN) responsible for task- and attention-switching. Thus, a reliable within-DMN and between-network connectivity may provide an opportune window for further exploring depression etiology. The current study examined correlations of spontaneous blood oxygen level dependent activity both within the DMN (ventral and core DMN subcomponents) and between-network (DMN – CCN subcomponents) over two time points in 82 individuals either with remitted (r) MDD (n = 47) or as Healthy Controls (HC; n = 35) to further classify the reliability of the networks and abnormalities in MDD. Linear Mixed Effects (LMEs) models showed that rMDD have a stable hyperconnectivity within DMN subcomponents and between cDMN and CCN subcomponents, but show no abnormality between vDMN and CCN subcomponents. In addition, rMDD showed more reliable connectivity over time than healthy controls, suggesting these network correlations are stable disease markers. The specificity of these findings has implications for future examinations of malleable treatment targets (i.e., vDMN – CCN connectivity) and stable disease markers that can identify those most at risk for developing the disorder (i.e., cDMN – CCN connectivity).

I. INTRODUCTION

A. Background

Major Depressive Disorder (MDD) is the second leading cause of disability in the world, without including comorbid disability attributed to suicide and heart disease (Ferrari et al., 2013). Not only does MDD carry a 16.5% lifetime prevalence rate in American adults (NIMH, 2013), each episode of depression in adolescence substantially increases the risk for subsequent episodes (Burcusa & Iacono, 2007) and enduring social and cognitive impairments (Alloy, Abramson, Whitehouse, & Hogan, 2006) including executive functioning (Snyder, 2013). Executive functioning recovers to an extent after a depressive episode has remitted, but the extent to which each episode leaves compounding scars on cognitive and executive functioning is still unknown (Hasselbalch, Knorr, & Kessing, 2011). Thus, earlier identification, etiological knowledge and treatment predictors are pertinent areas of continued research.

The search for these disease risk factors and course predictors has increasingly led to potential brain-based biomarkers of MDD (e.g., Broyd et al., 2009). In particular, neuroimaging studies of functional connectivity in depression have reported hyperconnectivity within the Default Mode Network (DMN; e.g., Whitfield-Gabrieli & Ford, 2012) and between the DMN and the Cognitive Control Network (CCN; e.g., Stange, Bessette, et al., 2017). The DMN is involved in many different functions concerning the self, remembering the past, and planning for the future (Raichle et al., 2001). The CCN is involved in functions important for the executive control of attention, and modulates the activation and suppression of the DMN based on task and self-generated demands (Andrews-Hanna, Smallwood, & Spreng, 2014). Several theories posit that individuals with depression are less likely (or able) to rely on the CCN's regulatory functions over the DMN, possibly due to increased effort or energy costs (S. A. Langenecker, Jacobs, & Passarotti, 2014; Wang, Ongur, Auerbach, & Yao, 2016).

The result of this imbalance is increased communication across networks, decreased communication within networks, and maintenance of the pathophysiology of MDD.

Individuals with depression show hyperconnectivity of DMN with dorsal attention and frontoparietal network subcomponents of the CCN (Erk et al., 2010; Jacobs et al., 2016; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Sheline, Price, Yan, & Mintun, 2010) as well as ventral attention and limbic networks (e.g., Connolly et al., 2013; Manoliu et al., 2013; Sheline et al., 2010; Wang et al., 2016; Zeng et al., 2012). Aberrant ventral attention and limbic connectivity with DMN are closely related to severity of depression (Hwang et al., 2016), thus more closely related to the active phase of depression and likely a state-specific disconnection rather than a trait of the disorder. In contrast, dorsal attention and frontoparietal networks show increased connectivity with the DMN in those with depressive illness reproducible across mood states (Jacobs et al., 2014; Zhong, Pu, & Yao, 2016). Of note, repetitive transcranial magnetic stimulation applied to left dorsolateral prefrontal cortex, a primary hub or node of the CCN, in those with active MDD modulates interactions between DMN and CCN such that subsequent decreased connectivity between these networks was associated with greater clinical efficacy of treatment (Fox, Buckner, White, Greicius, & Pascual-Leone, 2012; Liston et al., 2014). If decreased connectivity between these networks is associated with remission, then increased connectivity between CCN and DMN networks may serve as a maintenance factor for depressive illness and recurrence.

While hyperconnectivity of the DMN has been observed in depressed young (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015) and older adults (Zhu, Li, Wang, & Li, 2014) and remitted young adults (Jacobs et al., 2014), conflicting work shows hypoconnectivity of the DMN in first-episode depressed (Chen, Wang, Zhu, Tan, & Zhong, 2015) and recurrent older adults (Manoliu et al., 2013). Discrepant findings such as these suggest that variability in these relatively small samples may be

masking true effects of the depressive illness. A more nuanced effect is thus likely, such that some aberrant connectivity findings change based on mood state, episode or developmental phase. In addition, analyses of aberrant DMN connectivity in depression have tended to center around large hubs or nodes of these networks, such as the posterior cingulate cortex and medial prefrontal cortex within the DMN, rather than examining the integrity of network connections as a whole. Examination of specific hubs based on previous research increases chances of Type II error rates, whereas whole network examinations increase variability and reduce the chance for significant findings. Controlling for various confounding factors and using network subcomponents for more nuanced modeling are important next steps in understanding aberrant functional connectivity associated with depression.

One way of examining aberrant within-DMN and between-network connectivity is through functional connectivity of resting-state magnetic resonance imaging (fc-rsMRI), which gives accurate estimations of correlations of brain activity across related regions and independent of any task. In healthy samples, the DMN and CCN are 2 of the most reliably found networks over 6 months (Zuo & Xing, 2014). Fc-rsMRI of the DMN in particular is moderately reliable within-participants on test-retest analyses (ICC = 0.45), and produces moderate to high group-level reproducibility and replicability (Shehzad et al., 2009; Wisner, Atluri, Lim, & Macdonald, 2013), even with variations in analytic methods, sample size and time scale (Guo et al., 2012). Brain-based biomarkers in both active and remitted depression have been detected using fc-rsMRI in both the DMN and CCN (e.g., Castellanos, Di Martino, Craddock, Mehta, & Milham, 2013), yet only one study to date has reported on the reliability of fc-rsMRI in depression. They found reliable hypoconnectivity between the dorsolateral prefrontal cortex and inferior parietal lobule (both CCN nodes) with the larger CCN network in individuals with rMDD compared to healthy controls (ICC = 0.82; Stange, Bessette, et al., 2017). Three other CCN nodes that were lower in rMDD at the first timepoint were not replicated.

B. Undue Influences on Connectivity

Notably, several lines of research have recently enquired into the influence of various external factors on fc-rsMRI findings. Many factors influence the quality of acquired functional MRI data in general, such as thermal noise, system noise in the scanner and physiological noise from the participant (Bennett & Miller, 2010), yet functional imaging variance is mostly due to large-scale stable differences between individuals rather than within-participant differences (Miller et al., 2009; Miller, Handy, Cutler, Inati, & Wolford, 2001; Miller et al., 2002). Even scanner differences appear minimal, leaving up to two-thirds of the variance in functional imaging results due to between-participant differences (Costafreda et al., 2007). Even so, factors such as participant movement during fc-rsMRI scanning and scanning length have larger impacts than previously expected (Birn et al., 2013; Ciric et al., 2017; Shah, Cramer, Ferguson, Birn, & Anderson, 2016). Aberrant DMN connectivity will be most useful in future clinical and research settings if various influences on this potential biomarker can be controlled for, either at the time of scanning or in subsequent preprocessing and analysis stages.

1. Time Between Scans

Although several studies have examined the test-retest reliability of fc-rsMRI in healthy samples, surprisingly few have reported the length of time between scans in test-retest designs. Most examining test-retest of fc-rsMRI have used the NYU TRT dataset (www.nitrc.org/projects/nyu_trt), composed of 25 healthy controls with three scans, a baseline followed by 2 within the same scan session 5 – 16 months later (Birn et al., 2013; Shehzad et al., 2009; Song et al., 2012). More recent analyses have broadened this work by examining network reproducibility over shorter time periods and more scans, ranging between every 3 days for 1 month to every week for 3.5 years (B. Chen et al., 2015; Choe et al., 2015; O'Connor et al., 2017). However, no analyses yet published have examined any fluctuations in reproducibility due to the amount of time between scans, either between subjects or

between scan sessions. While time between measurements clearly influences test-retest reliability, this effect has potentially more meaningful causes or consequences for functional connectivity in psychiatric populations. In MDD, influences on functional connectivity due to the amount of time between scans could be systematically related to mood-state fluctuations, treatment-induced or naturalistic improvements on mood or cognition, increased severity/number of symptoms, treatment or medication changes, increased scar burden or other biological changes that may affect mood and disease state (e.g., poor sleep, increased stressors or inflammation, etc.). In addition, it is unknown whether increased time between scans would reduce overall reliability of both within-DMN and between-networks connectivity, or whether it would affect specific network connections. It is thus imperative to examine whether this potentially confounding factor plays a role in the reliability and reproducibility of functional connectivity differences in depressed populations.

2. **Participant Movement**

The influence of participant head motion on fc-rsMRI has been a contentious topic. It is now recognized that head motion induces systematic artifact effects on connectivity results (Power, Schlaggar, & Petersen, 2015), and that participant movement is stable, trait-like (Zeng et al., 2014), and related to younger age (Satterthwaite et al., 2012) and increased trait impulsivity (Kong et al., 2014). In fact, greater head motion has been linked to decreased connectivity within regions of DMN and frontoparietal networks (Van Dijk, Sabuncu, & Buckner, 2012), particularly regions of greater distance (Zeng et al., 2014). Previously identified methods, such as using head realignment parameters as confounding regressors or scrubbing high-motion frames, do not fully remove the effects of head movement on the blood-oxygen-level dependent signal, effects that can last up to 10 seconds later (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Power et al., 2014). Several newer methods have been produced to reduce inter-individual differences caused by motion, such as global signal

regression and Z-standardization of subject-level maps, although the effectiveness of these methods are still debated (Ciric et al., 2017; C. G. Yan et al., 2013). Indeed, even micromovements are related not only to spurious connectivity findings, but also to specific psychiatric illnesses (Greicius, 2008), potentially confounding results of group differences. Sampling biases can occur when motion is corrected by excluding participant movement outliers, particularly when motion is correlated with group differences such as diagnosis (Wylie, Genova, DeLuca, Chiaravalloti, & Sumowski, 2014). Finally, the reliability of fc-rsMRI is significantly affected by motion (C. G. Yan et al., 2013), suggesting any reproducible findings must be examined for undue influence of participant head motion.

C. **Purpose of This Study**

The current study examines within-DMN and DMN with CCN (between-networks) connectivity to determine diagnostic differences in network correlations between healthy young adults and those with remitted MDD while controlling for multiple influential factors. Scan session, days between scans and participant head motion are examined for undue influences on diagnostic functional connectivity differences. Young adults were chosen to avoid variability associated with developmental differences in functional connectivity architecture. Those in remission from depression were selected to avoid the additional scar burden that may result from more depressive episodes, and mood state effects that may be attributable only to the acute phase of the illness. In addition, mood state effects are less likely to play a significant role over time in remitted compared to active depression, increasing the opportunity for finding stable diagnostic-specific differences in connectivity. Finally, rather than examine specific hubs, this study examines correlations of connectivity between network subcomponents defined from a parcellation map standardized on 1,000 healthy adults (Yeo et al., 2011). Specific aims and hypotheses are as follows:

1. **Aim 1**

Identify within-DMN and between-networks functional connectivity correlation differences in rMDD compared to healthy controls (HCs) across two scan sessions within a linear mixed effects model analysis. Seven networks connections were chosen from a standardized 17 network parcellation map (Yeo et al., 2011), one between subcomponents of DMN (ventral and core) and 6 between these DMN subcomponents and 3 CCN subcomponents (lateral frontoparietal, dorsal frontoparietal, and anterior frontotemporal).

Hypotheses: In line with previous research, rMDD will show hyperconnectivity within DMN and between DMN and specific subcomponents of CCN (frontoparietal networks; FPN) compared to HCs.

2. **Aim 2**

Evaluate whether correlations within DMN and between DMN and CCN change over time and whether this change differs based on diagnosis.

Hypotheses: Because rMDD will either continue or increase in residual depressive symptoms over time between scans, correlations within DMN and between DMN and CCN will show no changes over time within individuals with rMDD. HCs are less likely to show systematic changes that would confound connectivity results, thus are predicted to show no changes over time in any of the examined network connections.

3. **Aim 3**

Determine if technical variables of total participant movement translations and the number of days between scan sessions unduly influence specific network connectivity correlations.

Hypotheses: Specific network connectivity correlations will not be influenced by the number of days between scan sessions. In line with the literature, participant movement will influence broadly all network correlations of interest.

II. METHODS

A. Design

The current study is a longitudinal assessment of young adults either in remission from depression (rMDD) or healthy controls (HC) recruited from both the University of Michigan (UM) and the University of Illinois at Chicago (UIC). Both sites' Institutional Review Boards approved this study. The current study was part of a larger protocol including a comprehensive battery of neuropsychological tests, self-report measures, and structural and functional magnetic resonance imaging (MRI), much of which is reported elsewhere.

B. Procedure

Trained research assistants first screened participants over the phone to ensure participants met inclusion criteria. At the first visit, written informed consent was obtained prior to master's-level clinicians conducting a Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) to determine prior diagnosis and remission from MDD. A separate interview with a consenting family member (Nurnberger et al., 1994) was conducted by phone or in-person to confirm diagnosis and family history. Participants came back for a brief medical examination to assess contraindications and safety for MRI procedures. Qualified participants underwent a 2 hour functional and structural MRI scan, which included tasks such as the Facial Emotion Perception Task (S. A. Langenecker, Zubieta, Young, Akil, & Nielson, 2007), Semantic List-Learning Task (Schallmo et al., 2015), Parametric Go/No-Go Task (S. A. Langenecker et al., 2007), a resting-state scan and structural scans. The second scan was scheduled at a later time convenient for participants, usually about 2 months later.

C. Participants

Participants recruited to this study were between the ages of 18 – 23. Females were oversampled to better approximate gender discrepancy in young adults affected by depression (Nolen-

Hoeksema, 2001). Exclusion criteria included standard MRI contraindications (e.g., metal in the body), loss of consciousness greater than 10 minutes, serious medical conditions (e.g., diabetes), and substance abuse or dependence within the last 6 months. Healthy controls were required to be free from meeting current or past criteria for any Axis I or II DSM-IV-TR psychiatric disorder in addition to their first-degree relatives. rMDD were excluded from current analyses if self-report scores indicated clinically significant residual depression or anxiety symptoms at intake (HDRS > 8, HAM-A > 10; M. Hamilton, 1960, 1969). In addition, only participants with 2 completed resting-state scans were included in the current analyses.

D. fMRI Protocol

At UM, an eyes-open resting-state scan was acquired over eight minutes on a 3.0T GE Signa scanner (Milwaukee, WI) using T2-weighted single shot reverse spiral sequence (flip angle = 90°, field-of-view = 20 cm, 64 x 64 matrix, slice thickness = 4 mm, echo time = 30 ms, 29 slices). At UIC, eyes-open, resting-state scans were collected over eight minutes on a 3.0T GE Discovery scanner (Milwaukee, WI) using parallel imaging with ASSET and T2 gradient-echo axial echo-planar imaging (flip angle = 90°, field-of-view = 22 cm, 64 x 64 matrix, slice thickness = 3 mm, echo time = 22.2 ms, 44 slices). At both sites, high-resolution anatomic T1 scans were obtained at each scan for spatial normalization. Subject motion was reduced by informing participants on the importance of staying still, using foam pads on the head, a visual tracking line (UIC only) and/or fixation cross (UIC and UM) on the display. Resting-state scans had TRs of 2000 ms length and 240 TRs in total at each site.

E. Image Preprocessing Procedures

Several steps were taken to reduce potential sources of noise and artifact, consistent with preprocessing procedures reported on subsets of this data elsewhere (Bhaumik et al., 2016; Jacobs et al., 2016; Jacobs et al., 2014; Rao et al., 2016) . SPM8 was used to complete slice timing

(http://www.fil.ion.ucl.ac.uk/spm/doc/) and FSL for motion detection (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Structural images were coregistered to functional images, followed by spatial normalization of the coregistered T1-spgr to the MNI template. This normalization matrix was then applied to the slice-time-corrected, physiologically-corrected, time series data. Then the normalized T2 timeseries data were spatially smoothed with a 5 mm Gaussian kernel. The resulting T2 images had 2 mm on each side of isotropic voxels.

F. **Definition of Functional Networks**

Network masks were defined using the 17 parcellation network map from functional connectomes of 1,000 healthy adults (Yeo et al., 2011). See Appendix for a view of the networks chosen. Two parcellations were designated as subcomponents of the DMN, specifically ventral and core DMN (Buckner, Andrews-Hanna, & Schacter, 2008). In addition, 3 parcellations that overlapped with the dorsolateral prefrontal cortex and were subcomponents of the CCN were chosen to test DMN – CCN connectivity patterns (Sheline et al., 2010). These subcomponents were labeled according to their spatial patterns, such that two had frontoparietal activity (lateral and dorsal frontoparietal networks; lFPN and dFPN, respectively) and one had frontotemporal activity (anterior frontotemporal network, aFTN). See Table 1 below for depiction of networks and labels used.

Table I
Networks used in the current study

Large Network	*Spatial Network*	*Spatial Location*	*Abbreviation*
Cognitive Control Network	Frontoparietal	Lateral	lFPN
		Dorsal	dFPN
	Frontotemporal	Anterior	aFTN
Default Mode Network		Core	cDMN
		Ventral	vDMN

G. Functional Connectivity Procedures

Time series data were detrended and mean-centered. Physiologic correction was performed by regressing out white matter and cerebral spinal fluid signals (Behzadi, Restom, Liau, & Liu, 2007). Motion parameters were regressed out (Jo et al., 2013). Based upon the recent literature, motion of 1.5 mm or more in any direction over 3 consecutive TRs was used as a gross criterion for participant exclusion from analyses (Jo et al., 2013; Power et al., 2012); any TR to TR movement exceeding 0.5 mm was also used as participant exclusion from analyses (Power et al., 2012). In addition, greater than 2 mm movement over an entire scan was also used as a criterion for participant exclusion from current analyses. Number of excluded participants did not differ by group. Final analyses were reconducted without those who were outliers based on movement deviation value across the entire time series in relation to the rest of the sample. Equal numbers of HC and rMDD tend to be identified and removed using these procedures (Jacobs et al., 2016).

Due to previous literature suggesting that global signal regression leads to colinearity violations with gray matter signal, that it creates problematic mis-estimations of anticorrelations (Fox, Zhang, Snyder, & Raichle, 2009) and because it distorts distance-micromovement relationships (Jo et al., 2013), global signal regression was not conducted. Time-series were band-pass filtered over 0.01 – 0.10 Hz. Movement was addressed, as mentioned previously, using regression of white matter and cerebrospinal fluid signals such as is recommended in the recent literature (Jo et al., 2013; Power et al., 2012). Correlation coefficients were calculated between mean time course for seed DMN networks and other networks. These correlation coefficients were transformed to Z-scores using a Fisher transformation.

H. Linear Mixed Effects Analyses

Resulting correlation coefficients were used in a diagnostic group by time linear mixed-effects (LME) analysis implemented in SPSS (v24.0) to account for the interdependence of each participant's network correlations and interdependence over time. To produce the most unbiased estimates of covariance parameters, restricted maximum likelihood estimation (REML) with Newton-Raphson iterative algorithms were used. All continuous variables included in analyses (i.e., days between scans, total head movement, and all network correlations) were examined for normality, two were logarithmically transformed to better approximate normality (Tabachnick & Fidell, 2007), and all were grand mean centered prior to analysis. All discrete variables included in analyses were dummy-coded.

Analyses were conducted such that the intercept represents cDMN – vDMN network correlations in rMDD at the first scan at UIC. Top-down LME analyses followed procedures suggested by Verbeke and Molenberghs (2009) and West, Galecki, and Welch (2015): (1) a two-level loaded mean structure was fit to the data including fixed effects, in order, of between-network connections, diagnosis, time, interaction of between-network connections and diagnosis, interaction of diagnosis and time, site and sex, with repeated effects of time by between-network connections and random effects of subject-specific intercept with between-networks connections; (2) best repeated-effects and random-effects covariance structures were determined by examining best fit using a combination of Akaike's Information Criterion (AIC) and Bayes Information Criterion (BIC) for typical covariance structures (diagonal, compound symmetry, first-order autoregressive, toeplitz; models that failed to converge or find a positive hessian matrix were excluded); (3) heterogeneous and homogeneous residuals over time were compared using AIC and BIC to determine best fit; (4) the model was reduced by removing all nonsignificant fixed effects except effects of primary interest (e.g., diagnosis and between-networks connections by diagnosis). The final best-fit LME included 21 parameters with fixed factors, in order, of intercept, between-network connections, diagnosis, time, between-network

connections by diagnosis, diagnosis by time, and site, with random effects of subject-specific intercept and between-network connections (compound symmetry covariance structure), along with repeated effects of time by between-networks connections (first-order autoregressive covariance structure). To examine model assumptions of normality, the final model's residuals and trends with predicted values were examined. Within the LME framework, significance of fixed effects of diagnosis and diagnosis by between-networks connections were evaluated to address Aim 1.

I. Reliability Analyses

Significance of fixed effects of time and time by diagnosis were examined within the LME model to address Aim 2. In addition, ICC values were computed from the unconditional mean LME model (with between-networks connections included as a fixed effect within individuals) to quantitatively measure the amount of variance attributable to between-subjects effects. In this way, it evaluates the need for controlling variance in the outcome by using an LME-based model (compared to traditional analyses of variance; Shek & Ma, 2011; Singer & Willett, 2003).

J. Potential Influences

To address the possibility of technical variables influencing the current findings, a post-hoc LME model was run on the loaded LME (prior to factor reduction) that included fixed effects of the participant-specific days between scans and time-specific total deviation in movement translation, as well as interactions of these with between-network connections. The resulting model's fit was compared to the fit of the loaded LME without these variables. Addressing Aim 3, significant fixed effects of participant-specific days and time-specific movement would suggest that these variables have a broad effect on overall measurement of network connectivity. Significant fixed effects of the interactions of these variables with between-network connections would suggest these technical variables have an undue influence on specific network correlations.

III. RESULTS

A. Participants

A total of 109 individuals meeting primary inclusion criteria completed the first fMRI scan. From this group, 27 participants were excluded from subsequent analyses for the following reasons: (1) Sixteen participants dropped out before the second scan could be completed or declined to complete the second scan, (2) one participant was excluded due to technical issues with MRI files, (3) one rMDD was excluded for psychotic symptomology during the intake interview, (4) seven rMDD were excluded for active depression at the first scan according to HDRS self-report and/or clinician diagnosis, and (5) two HCs were excluded for subsequent depressive/manic episodes. Thus, a total of 82 participants (35 HC and 47 rMDD), with 47 from the UM site (57.32%) and 55 females (67.07%), were included in the subsequent analyses. rMDD and HC did not show significant differences in demographic characteristics or IQ (all p's > .05; see Table II below). As expected, these diagnostic groups significantly differed by self-report of residual depressive symptoms, t (69.67) = -3.44, p = .001.

B. Movement and Time as Potential Influences

Movement is a well-known parameter that influences the outcomes and reproducibility of neuroimaging data, even after extensive motion correction applied in preprocessing and first-level models. In addition, the amount of time that passes between test-retest periods for any measure are also known to influence measurement reliability. To ensure there were no group-level effects from the current sample, t-tests and reliability analyses were conducted. There were no observed differences in the amount of days between MRI scans for the two diagnostic groups, t (80) = -0.02, p = .98. Additionally, there were no observed differences between movement translations in any direction in either scan across diagnostic groups (all p's > .30; see Table III below). Individual-specific

Table II
Participant Demographic and Clinical Characteristics

Characteristics	HC (n = 35) M (SD)	rMDD (n = 47) M (SD)	t	p
Age at First Scan	21.45 (1.67)	22.16 (1.53)	1.99	.05
Years Education	14.54 (1.36)	14.66 (1.29)	0.40	.69
Gender (% Female)	60.00	72.30	$\chi^2 = 0.13$	.24
Site (% UM)	37.10	34.00	$\chi^2 = 0.03$	.77
Ethnicity (% Hispanic)	11.40	8.50	$\chi^2 = 0.05$	.66
Race (% Caucasian)	80.00	70.20	$\chi^2 = 0.16$	.51
Handedness (% Left)	5.70	8.50	$\chi^2 = 0.11$	.60
Age of Onset	-	16.61 (3.45)	-	-
Years in Remission	-	2.72 (1.72)	-	-
Number Previous Episodes	-	1.76 (1.12)	-	-
Verbal IQ (N = 81)	105.86 (9.27)	106.67 (10.48)	0.37	.72
HDRS [a,b]	0.43 (1.01)	1.64 (2.11)	3.44	**.001**

Note. HDRS, Hamilton Depression Rating Scale; HC, Healthy Control; rMDD, Remitted Major Depressive Disorder.
[a] $g_{Hedges} = 0.69$.
[b] Levene's test significant ($F = 24.16$, $p < .001$), thus degrees of freedom are adjusted.

reliability of movement translations over time range from poor to good (i.e., 0.30 – 0.82). Boxplots of movement translations by diagnosis revealed 10 rMDD and 10 HC with movement translation outliers on at least one parameter for one fMRI scan (see Figure 1). The final LME model was re-run without these outliers to determine whether effects were stable. The results of this model are reported in the appropriate section below.

C. **Fitting a Linear Mixed Effect Model**

Information criteria (best fit measures of -2 Restricted Log Likelihood and Akaike's Information Criterion), and number of parameters are reported in Table IV at each model decision. The original two-level loaded mean unstructured model was simplified best by using a compound symmetry covariance structure for random effects of subject-specific intercept and between-networks connections and a first-order autoregressive covariance structure for repeated effects of time by subject-specific between-networks connections, -2RLL = -738.90, AIC = -730.90. This model used

Table III
Participant Scan-specific Movement Translation Deviations and Days Between Scans

Characteristics	HC (n = 35) M (SD)	rMDD (n = 47) M (SD)	*t*	*p*
Days Between Scans	54.46 (42.12)	54.66 (34.68)	-0.02	.98
Scan 1 (mm)				
x translation	0.05 (0.05)	0.06 (0.05)	-0.94	.35
y translation	0.05 (0.05)	0.05 (0.04)	0.26	.80
z translation	0.19 (0.16)	0.16 (0.19)	0.77	.44
Scan 2 (mm)				
x translation	0.05 (0.04)	0.05 (0.05)	-0.24	.81
y translation	0.04 (0.04)	0.05 (0.05)	-1.02	.31
z translation	0.15 (0.14)	0.17 (0.14)	-0.78	.44
Reliability[a] *(ICC)*				
x translation	0.47	0.60		
y translation	0.82	0.48		
z translation	0.30[b]	0.45		

Note. Movement deviations are the standard deviations of the realignment adjustments over the 8 minute resting state scan.
[a] Reliability of movement ICC for all participants was 0.56[c], 0.66, and 0.38 for x, y, and z translations, respectively.
b Not significantly different from zero at $p < .05$.

fewer parameters and had a lower -2RLL fit compared to other positive definite structured models that converged. The homogeneous residual variance model fit better than heterogeneous residual variance model and used fewer parameters, χ^2 (6) = -92.84, $p > .95$, thus homogeneous residual variances were kept in subsequent models. This homogeneous residual variance model indicated no significant fixed effects of between-networks connections over time, F (6, 381.26) = 0.52, p = .80, nor sex, F (1, 77.98) = 0.89, p = .35, thus these were both dropped from the next model. Although the fixed effect of between-networks connections by diagnosis was not significant, F (6, 468.87) = 1.88, p = .08, this effect was a primary hypothesis of the current study and showed trend-level significance thus was included in the subsequent model. This last model used fewer parameters and showed better -2RLL fit without those two variables, χ^2 (7) = 35.45, $p < .01$. A total of 21 parameters and 51 levels were

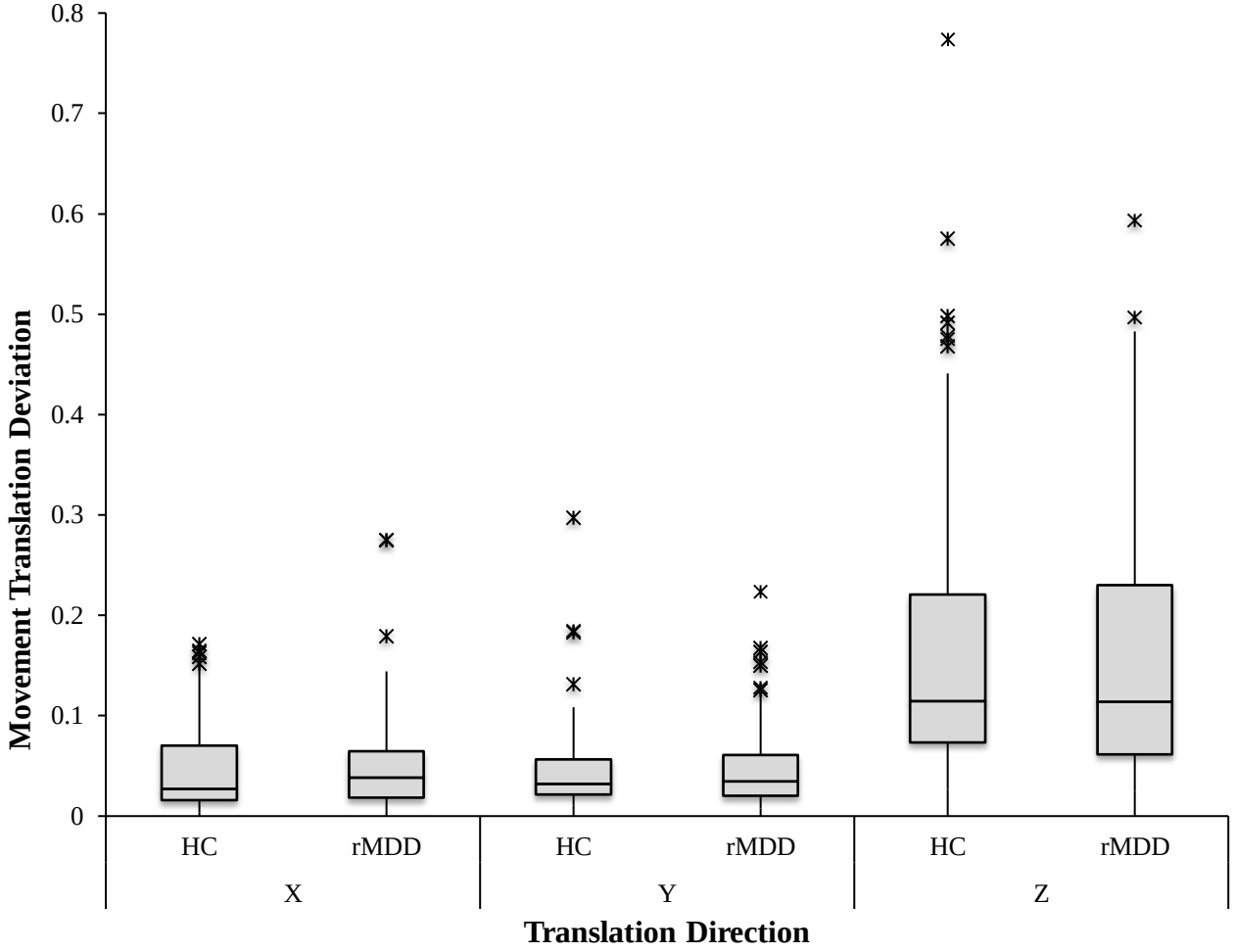

Figure 1. Boxplots of the standard deviation of head movement in x, y and z directions for both diagnostic groups, collapsed across scan sessions. Outliers are indicated with asterisks.

included in this final model, which showed better AIC than all previous models, AIC = -766.35. Examination of residuals from this final model revealed a relatively normal distribution, SD = 0.12, with skewness of -0.07 (0.07) and kurtosis of -0.11 (0.14). In addition, residuals showed a small linear trend with predicted values, accounting for only 3.50% of the variance (y = 0.09 x - 0.02), suggesting the current model and distributions adequately met assumptions of LMEs.

Table IV
Information Criteria and Parameters for Significant Model Decisions

Model	Fixed Effects	Random Structure	Repeated Structure	Parameters	-2RLL	AIC	BIC
(1) Original[a]	Full Model[b]	UN	UN	157	-1231.80	-365.14	-297.54
	Full Model	Diagonal	AR1	33	-703.08	-685.08	-639.86
	Full Model	AR1	AR1	28	-694.58	-686.58	-666.48
	Full Model	AR1	CS	28	-671.29	-663.29	-643.19
(2a) Homo[c]	Full Model	CS	AR1	28	-738.90	-730.90	-710.80
(2b) Hetero[c]	Full Model	CS	AR1	34	-646.06	-638.06	-617.98
(3) Final	Significant Only[d]	CS	AR1	21	-774.35	-766.35	-746.23

Note. AIC = Akaike's Information Criterion, AR1 = First-Order Autoregressive, BIC = Bayes Information Criterion, CS = Compound Symmetry, -2RLL = -2 Restricted Log Likelihood, UN = unstructured.
[a] Original model with maximum fit due to complete unstructured covariances did not result in a positive definite hessian matrix. All other non-convergent or non-positive definite hessian matrices are not reported.
[b] Full Model included all fixed effects (between-network connections, diagnosis, time, interaction of between-network connections and diagnosis, interaction of diagnosis and time, site and sex).
[c] Homogeneous and heterogeneous residual covariance structures, respectively.
[d] Also includes theoretically-relevant fixed effect of the interaction of between-network connections and diagnosis, significant at trend levels, $p = .08$.

1. **Final Connectivity Linear Mixed Effect Model**

The final LME model included 7 fixed factors, 1 random effect (subject intercept with between network connections) and 1 repeated effect (time by between network connections). Six fixed factors were significant at *a priori* $p < .05$ (see Table V below). Correlations between DMN and CCN subcomponents were significantly lower than correlations between the two DMN subcomponents, $F(6, 469.15) = 274.58$, $p < .001$, with the notable exception of correlations between aFTN and cDMN, $\beta = -0.01$ (0.03), $t(554.20) = -0.20$, $p = .84$. Time was a significant fixed effect, $F(1, 246.06) = 6.66$, $p = .01$. Time effects were stronger in HCs, $F(1, 246.06) = 5.76$, $p = .02$, such that HCs showed increased correlations between networks over time, $\beta = 0.05$ (0.02), $t(246.06) = 2.40$, $p = .02$, but rMDD did not

Table V
Linear mixed model test of fixed effects of all networks in final model with first-order autoregressive repeated and compound symmetry random covariance structures

Type of Effect	Effect	df	*F*	*p*
Fixed	Intercept[a]	1, 102.01	0.02	0.90
	Between-Network Correlations	6, 469.15	274.58	< **.001**
	Diagnosis	1, 104.10	4.05	**.047**
	Time	1, 246.06	6.66	**.01**
	Between-Network Correlations By Diagnosis	6, 469.15	1.88	.08
	Diagnosis By Time	1, 246.06	5.76	**.02**
	Site	1, 78.98	12.43	**.001**
	Effect	β-Estimate	S.E.	*p*
Repeated Covariance	AR1 Diagonal	0.02	0.001	< **.001**
	AR1 Rho	0.34	0.04	< **.001**
Random Covariance	CS Diagonal Offset	0.01	0.001	< **.001**
(Intercept + Network Connections)	CS Covariance	0.0003	0.001	.64

Note. AR1 = First-Order Autoregressive, CS = Compound Symmetry.
[a] Intercept represents the mean correlation between ventral and core default mode network for remitted Major Depressive Disorder at Scan 1 at University of Illinois at Chicago.

show significant changes of correlations between networks over time, β = 0.002 (0.01), t (246.06) = 0.14, p = .88. Site also showed a significant fixed effect, F (1, 78.98) = 12.43, p = .001, such that those scanned at UM had greater correlations between all networks, β = 0.09 (0.03), t (78.98) = 3.52, p = .001.

Overall, correlations between networks were significantly different between diagnostic groups, F (1, 104.10) = 4.05, p = .047. Not all correlations between networks were different between diagnostic groups however, F (6, 469.15) = 1.88, p = .08. Differences between diagnostic groups were specific to correlations between lFPN and both DMN subcomponents, ventral: t (503.49) = -2.15, p = .03; core: t (545.80) = -2.66, p = .01, with trend-level differences between aFTN – cDMN and dFPN – cDMN networks, t (554.20) = -1.93, p = .05; t (436.82) = -1.94, p = .05, respectively. Beta estimates for all fixed effects compared to the mean correlation between ventral and cDMN at Scan 1 in the

rMDD group at UIC are listed in Table VI, depicted averaged over scan sessions in Figure 2, and depicted across scan sessions in Figure 3 below.

2. **Intraclass Correlation Reliability**

From the unconditional mean model, while controlling for within-subject effects due to measurements of several network connections, 35.7% of the total variation in all network correlations was due to interindividual differences. Thus, an LME model was appropriate for this sample's data.

Table VI
Estimated Fixed Effects of Final Model

Effect	*β*-estimate	*S.E.*	df	*t*	*p*
Intercept (Ventral – Core DMN)	0.28	0.03	249.16	10.72	< **.001**
Between-Network Correlations					
Lateral FPN – Ventral DMN (12 – 15)	-0.38	0.03	503.49	-13.93	< **.001**
Lateral FPN – Core DMN (12 – 16)	-0.33	0.03	545.80	-11.75	< **.001**
Anterior FTN– Ventral DMN (13 – 15)	-0.34	0.03	550.37	-12.06	< **.001**
Anterior FTN – Core DMN (13 – 16)	-0.01	0.03	554.20	-0.20	.84
Dorsal FPN – Ventral DMN (6 – 15)	-0.52	0.03	543.16	-18.89	< **.001**
Dorsal FPN – Core DMN (6 – 16)	-0.57	0.03	436.82	-22.15	< **.001**
Diagnosis (HC)	0.01	0.04	302.70	0.15	.88
Time (Scan 2)	0.002	0.01	246.06	0.14	.89
Between-Network Correlations By Diagnosis (HC)					
Lateral FPN – Ventral DMN (12 – 15)	-0.09	0.04	503.49	-2.15	**.03**
Lateral FPN – Core DMN (12 – 16)	-0.11	0.04	545.80	-2.66	**.01**
Anterior FTN – Ventral DMN (13 – 15)	-0.03	0.04	550.37	-0.61	.55
Anterior FTN – Core DMN (13 – 16)	-0.08	0.04	554.20	-1.93	.05
Dorsal FPN – Ventral DMN (6 – 15)	-0.06	0.04	543.16	-1.40	.16
Dorsal FPN – Core DMN (6 – 16)	-0.08	0.04	436.82	-1.94	.05
Diagnosis By Time (HC at Scan 2)	0.05	0.02	246.06	2.40	**.02**
Site (UM)	0.10	0.03	78.98	3.53	**.001**

Note. Intercept represents the mean correlation between ventral and core Default Mode Network for remitted Major Depressive Disorder at Scan 1 at University of Illinois at Chicago, thus all beta values are in relation to this intercept. For example, negative beta values within Between-Network Correlations indicate lower connectivity in these networks in remitted at Scan 1 at University of Illinois at Chicago. DMN = Default Mode Network, FPN = Frontoparietal Network, FTN = Frontotemporal Network, HC = Healthy Control, UM = University of Michigan.

D. **Potential Influences**

1. **Influences Added to Model**

Four additional variables were added as fixed effects to the full model with first-order autoregressive repeated and compound symmetry random covariance structures, resulting in 13 fixed effects. Additional variables were: (1) subject-specific number of days between the first and second scan, (2) interaction of days between scans with between-networks connections, (3) total movement translation of each subject at each scan and (4) interaction of total movement translation with between-networks connections. Adding these 4 variables did not improve the fit of the model, -2RLL = -711.63,

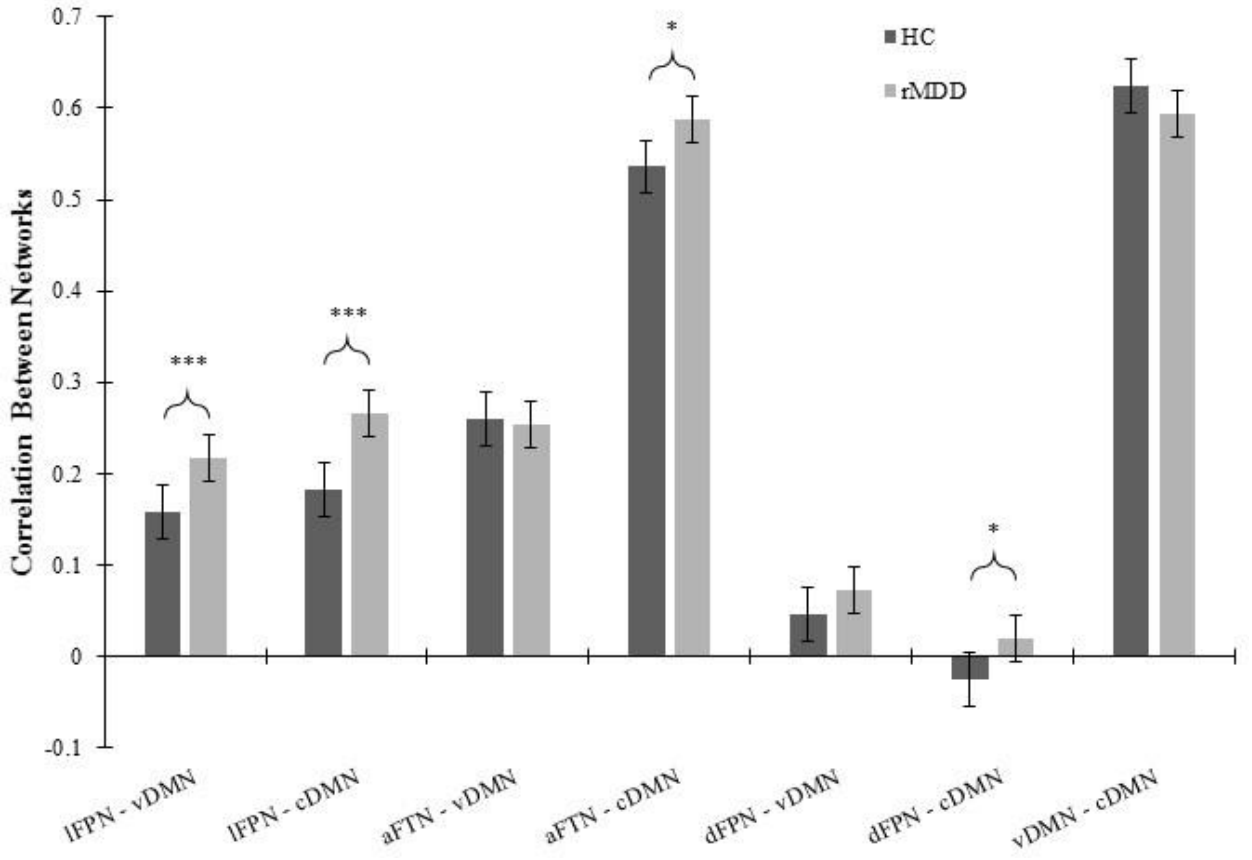

Figure 2. Estimated marginal means of correlations between networks collapsed over scan sessions compared across diagnostic group. Significant and trend-level differences between diagnostic groups are indicated by asterisks.
* $p < .10$; *** $p < .05$.

AIC = -703.63, BIC = -683.58. Variation in the days between scans was not a significant fixed effect, F (1, 76.15) = 0.71, p = .40, nor was the interaction of days between scans with between networks connections, F (6, 460.28) = 0.35, p = .91. However, scan-specific total movement translations was significant, F (1, 300.14) = 20.04, p < .001, suggesting that more movement corresponded to greater correlation between all networks, β = 0.04 (0.04), t (984.41) = 0.93, p = .35, but the interaction with specific between-network connections was not significant, F (6, 728.85) = 1.62, p = .14.

2. **Removal of Movement Outliers**

Scan-specific movement outliers identified from boxplots (see Figure 1) were removed from the final

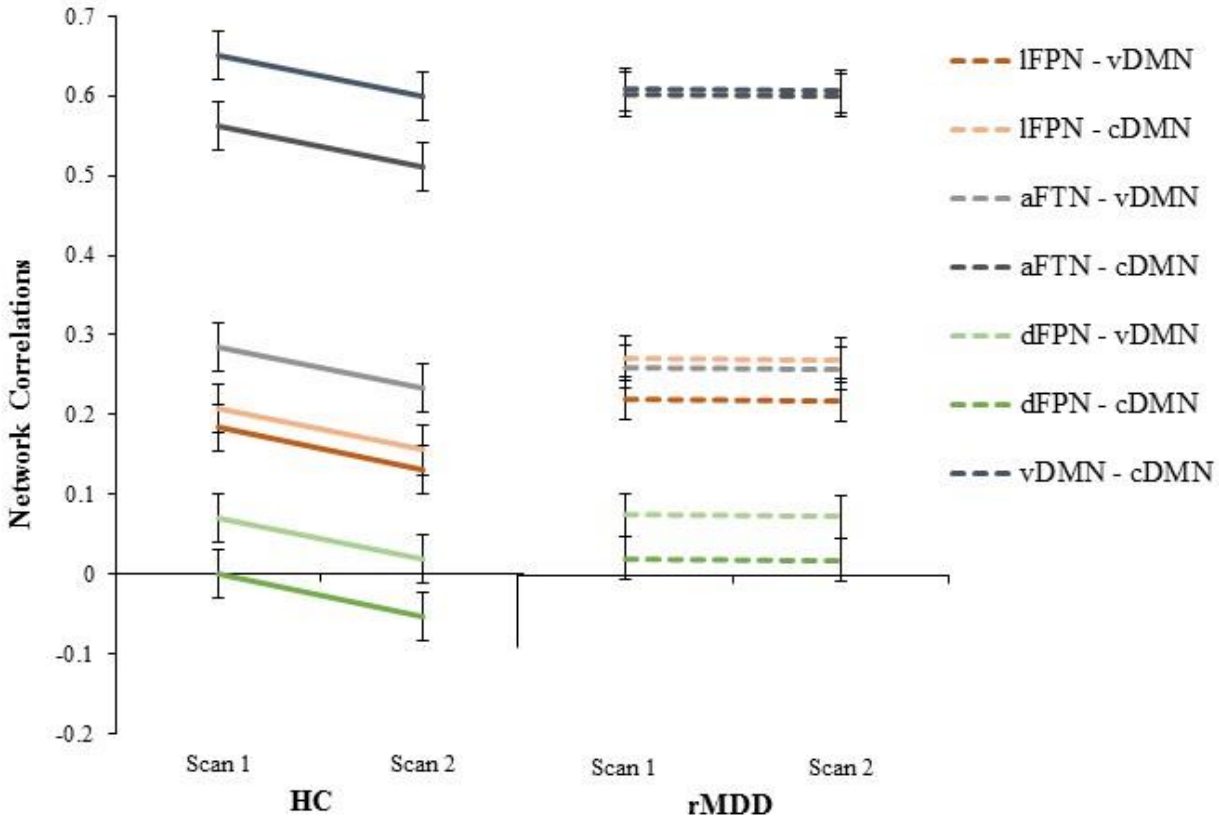

Figure 3. Estimated marginal means from final LME model of correlations between networks over both scans within each diagnostic group. Error bars represent standard error of the mean.

LME model (scans: n = 23). This resulted in a LME model with 79 subjects, some of whom had only one scan (n = 20). Results of this analysis were similar, albeit with decreased significance across fixed effects and decreased fit, -2RLL = -640.07, AIC = -632.07, BIC = -612.56, due to loss in sample size and power. Examination of residuals from this model revealed a relatively normal distribution, SD = 0.11, with skewness of -0.05 (0.08) and kurtosis of -0.11 (0.16). Residuals showed the same linear trend with predicted values, accounting for 4.10% of the variance (y = 0.09 x - 0.002), suggesting the current model and distributions adequately met assumptions of LMEs.

IV. DISCUSSION

The main goal of this study was to examine whether correlations within DMN and between DMN and CCN subcomponents stably differ over time between healthy young adults and those in remission from depression. We hypothesized rMDD would show higher correlations within DMN and between DMN and CCN, stable over time. Indeed, results suggest that correlations between core and ventral DMN and between both DMN subcomponents and lFPN were higher in individuals with rMDD than HCs. In addition, we observed trending differences between cDMN and aFTN and dFPN such that individuals with rMDD showed higher correlations between these networks than HCs.

These findings replicate and expand upon previous work documenting increased connectivity within DMN and between DMN and CCN in active, subthreshold and remitted MDD samples (Hwang et al., 2015; Jacobs et al., 2016). This hyperconnectivity within and between networks may thus be an important treatment or prevention target for depression. In addition to reproducing this hyperconnectivity in a remitted sample, the current study also documents that this connectivity difference from healthy samples is stable over time within the remitted state. Thus, hyperconnectivity within the DMN and between DMN and CCN can be found during the active phase (Kaiser et al., 2015; Sheline et al., 2010) and is stable in the remitted phase, suggesting it may be a biomarker or trait of the depressive illness. In combination with hyperconnectivity between right middle frontal gyrus and several nodes of the DMN (i.e., medial frontal gyrus, superior temporal gyrus) at remission contributing to predicting depressive relapse over the following year (S. Langenecker et al., under review), these results suggest that DMN-CCN hyperconnectivity may be an important target for secondary prevention.

The current study also emphasizes the subcomponent network level of diagnostic differences in connectivity. That is, rMDD hyperconnectivity is not solely due to one or two simultaneously

overactive hubs. Certainly, there may be excessively connected hubs between CCN and DMN, as other studies have indicated (Fransson & Marrelec, 2008; Hagmann et al., 2008; Sheline et al., 2010). However, those in remission have hyperconnectivity between both ventral and core subcomponents of DMN and between these subcomponents of DMN and lFPN (Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2014). This is an important distinction, particularly when considering the specificity of aberrant DMN connectivity with lFPN. This subcomponent of CCN indicates a portion of dorsolateral prefrontal cortex somewhat consistent with repetitive transcranial magnetic stimulation MDD intervention studies (Fox et al., 2012). This treatment traditionally targets dorsolateral prefrontal cortex with the hypothesis that stimulation to this location will reduce CCN connectivity with the DMN (Liston et al., 2014). While it is possible that either targeting a specific hub may reduce aberrant connectivity throughout both network subcomponents or treatment efficacy does not rely on a reduction in aberrant connectivity throughout both network subcomponents, these remain important empirical questions.

It is notable that connectivity across all examined networks decreased over scanning sessions, but only in HCs. This unexpected finding could be due to multiple different factors that the current analyses cannot tease apart and thus will need to be explored in future work. One potential factor involved in connectivity reduction in HCs over time may be a diagnostic-specific decrease in anxiety or other mood-related effects regarding the MRI environment (e.g., Tian et al., 2016), even though individuals with rMDD are more likely to experience anxiety in general (Pini et al., 1997). Because we did not anticipate these effects, we did not assess this sample for previous experience in MRI environments, nor changes in mood, anxiety or other related factors at the time of both scans. Within our protocol, we had monitored all participants during scanning for excessive motion or indications of sleeping and had excluded these participants from the current analyses, thus these two factors would

not account for the changes seen in connectivity. In addition, it is possible that change in connectivity over time is reflective of greater cognitive flexibility in thought patterns in HCs (Stange, Alloy, & Fresco, 2017). Indeed, much prior work has shown that negative, repetitive self-referential thoughts such as rumination are stable over time in both the active and remitted phase of depression (Beevers, Rohde, Stice, & Nolen-Hoeksema, 2007) and are associated with DMN activity and connectivity (J. P. Hamilton, Farmer, Fogelman, & Gotlib, 2015). Reasons for changes in network connectivity remain an active area of investigation for this field.

Several other notable factors influenced correlations between networks. Those who completed scanning procedures at UM displayed greater correlations between all networks. Site was included as a fixed effect due to previously known cohort demographic differences, including race and IQ (Jenkins et al., 2016), as well as differences in scanner mechanics (e.g., reverse spiral versus echo planar parallel imaging; Glover, 2012). While the amount of days between scan sessions did not significantly influence the model, total deviation in movement translations had a significant effect, showing increased correlations between networks with increasing head motion. The sample had already excluded participants with excessive head motion, thus this effect emphasizes the influence that micromovements can impart on connectivity analyses (C.-G. Yan et al., 2013). However, decreased connectivity within DMN and CCN due to motion has been found previously (Van Dijk et al., 2012), thus the direction of these effects were unexpected. Importantly, controlling for diagnostic differences in connectivity held when controlling for site and motion effects, demonstrating reproducibility over different samples, scanning parameters, and motion micromovements.

There are several important limitations worth considering in the context of this study. Individuals with rMDD showed significantly more depressive symptoms at baseline, an expected result due to depression history. Even in remission, many individuals continue to experience clinically

subthreshold levels of low mood, anhedonia, and especially sleep disturbance (Conradi, Ormel, & de Jonge, 2011). The current study was unable to examine mood and depressive symptom changes over time that may contribute to individual changes in connectivity patterns. While it is possible that the results found here are associated with residual depressive symptoms rather than the depressive illness, there are a few factors that make it more likely these findings are due to depression history. The reliability of hyperconnectivity over time and the lack of effects of time within the rMDD sample emphasize that this aberrant connectivity in depression does not change over time. In addition, the current study cannot rule out a potential effect of scar burden – that is, aberrant connectivity may be a result of the depressive episode rather than a trait marker of the illness (e.g., Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012). Future work will need to tease out this possibility by examining connectivity prior to the onset of any depressive episodes. Finally, the current study purposefully recruited a relatively homogenous sample to reduce several sources of variation: restricted age range to avoid developmental variations in connectivity, fewer depressive episodes to avoid excessive scar burden, and more females to approximate the gender effect. While the current findings show that aberrant connectivity in remitted depression is stable over time within this sample, this effect remains to be tested in more heterogeneous samples.

The current study suggests that hyperconnectivity within the DMN and between DMN and lFPN are reliable biomarkers of the depressive illness. Important future research is needed to determine whether this biomarker can be found in the same individuals before, during and after depressive episodes to fully determine whether this biomarker is a risk factor or consequence of the disorder. Finally, tying this biomarker with other aspects of depression, such as rumination or cognitive flexibility, will expand its utility as a treatment or prevention target within both psychotherapeutic and neuromodulation treatment trials.

APPENDIX

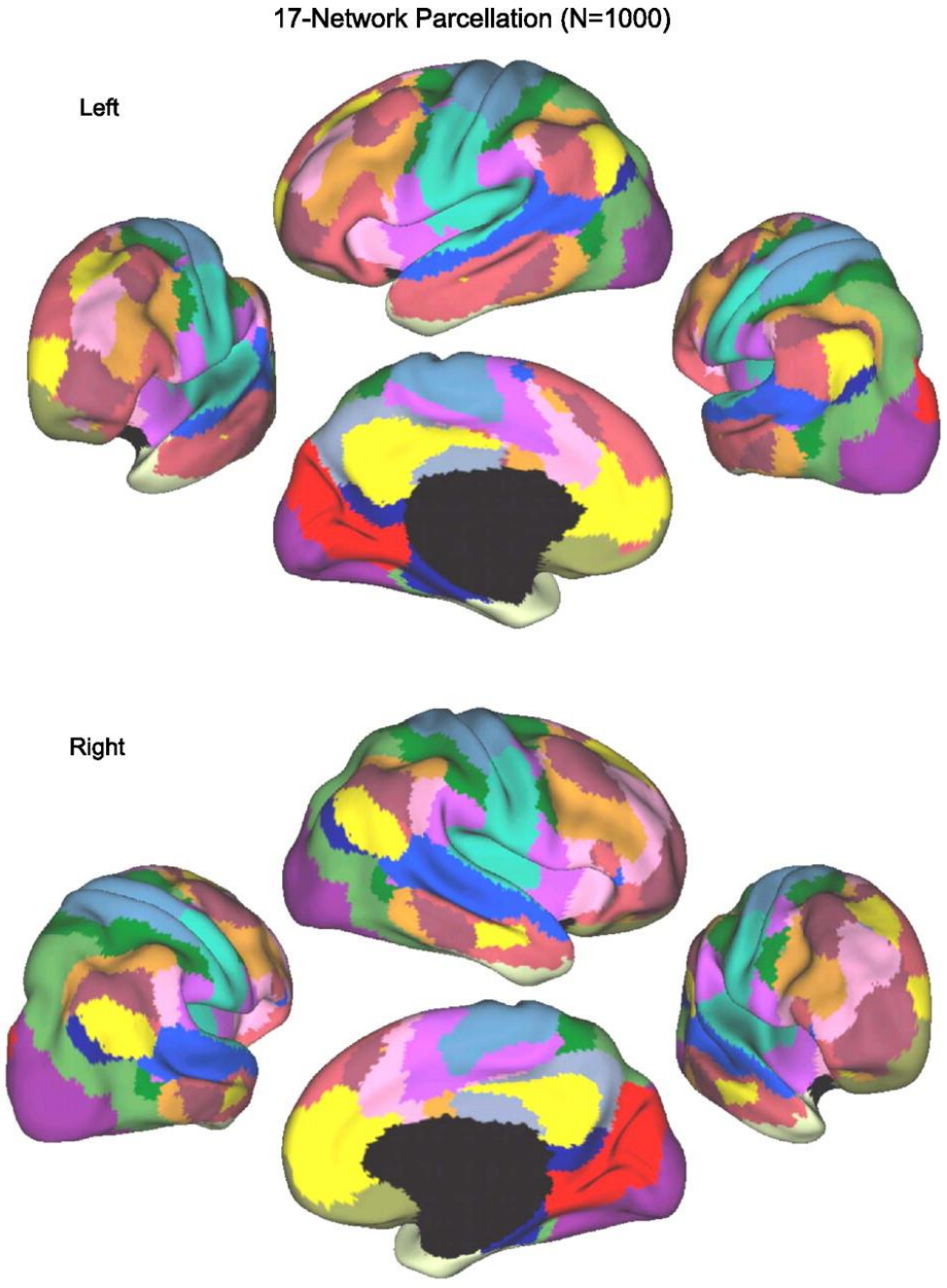

Figure 13 reprinted from Yeo et al. (2011). Analyses conducted within the current study focused on correlations of the DMN, depicted here in yellow (Core) and dark blue (vDMN), with subcomponents that encompassed dorsolateral prefrontal cortex, notably CCN subcomponents depicted in dark green (dFPN), orange (lFPN), and mauve (aFTN). Reprinted from the *Journal of Neurophysiology*: "**Theses and dissertations**. APS permits whole published articles to be reproduced without charge in dissertations and posted to thesis repositories. Full citation is required."

CITED LITERATURE

Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., & Hogan, M. E. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *Journal of abnormal psychology, 115*(1), 145-156. doi:10.1037/0021-843x.115.145

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Ann N Y Acad Sci, 1316*, 29-52. doi:10.1111/nyas.12360

Beevers, C. G., Rohde, P., Stice, E., & Nolen-Hoeksema, S. (2007). Recovery from major depressive disorder among female adolescents: A prospective test of the scar hypothesis. *Journal of consulting and clinical psychology, 75*(6), 888.

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage, 37*(1), 90-101. doi:10.1016/j.neuroimage.2007.04.042

Bennett, C. M., & Miller, M. B. (2010). How reliable are the results from functional magnetic resonance imaging? *Ann N Y Acad Sci, 1191*, 133-155. doi:10.1111/j.1749-6632.2010.05446.x

Bhaumik, R., Jenkins, L. M., Gowins, J. R., Jacobs, R. H., Barba, A., Bhaumik, D. K., & Langenecker, S. A. (2016). Multivariate pattern analysis strategies in detection of remitted major depressive disorder using resting state functional connectivity. *NeuroImage: Clinical*. doi:10.1016/j.nicl.2016.02.018

Birn, R. M., Molloy, E. K., Patriat, R., Parker, T., Meier, T. B., Kirk, G. R., . . . Prabhakaran, V. (2013). The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage, 83*, 550-558. doi:10.1016/j.neuroimage.2013.05.099

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. (2009). Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev, 33*(3), 279-296. doi:10.1016/j.neubiorev.2008.09.002

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38. doi:10.1196/annals.1440.011

Burcusa, S. L., & Iacono, W. G. (2007). Risk for recurrence in depression. *Clin Psychol Rev, 27*(8), 959-985. doi:10.1016/j.cpr.2007.02.005

Castellanos, F. X., Di Martino, A., Craddock, R. C., Mehta, A. D., & Milham, M. P. (2013). Clinical applications of the functional connectome. *Neuroimage, 80*, 527-540. doi:10.1016/j.neuroimage.2013.04.083

Chen, B., Xu, T., Zhou, C., Wang, L., Yang, N., Wang, Z., . . . Weng, X. C. (2015). Individual Variability and Test-Retest Reliability Revealed by Ten Repeated Resting-State Brain Scans over One Month. *PLoS One, 10*(12), e0144963. doi:10.1371/journal.pone.0144963

Chen, Y., Wang, C., Zhu, X., Tan, Y., & Zhong, Y. (2015). Aberrant connectivity within the default mode network in first-episode, treatment-naive major depressive disorder. *J Affect Disord, 183*, 49-56. doi:10.1016/j.jad.2015.04.052

Choe, A. S., Jones, C. K., Joel, S. E., Muschelli, J., Belegu, V., Caffo, B. S., . . . Pekar, J. J. (2015). Reproducibility and Temporal Structure in Weekly Resting-State fMRI over a Period of 3.5 Years. *PLoS One, 10*(10), e0140134. doi:10.1371/journal.pone.0140134

Ciric, R., Wolf, D. H., Power, J. D., Roalf, D. R., Baum, G. L., Ruparel, K., . . . Satterthwaite, T. D. (2017). Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *Neuroimage*. doi:10.1016/j.neuroimage.2017.03.020

Connolly, C. G., Wu, J., Ho, T. C., Hoeft, F., Wolkowitz, O., Eisendrath, S., . . . Yang, T. T. (2013). Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. *Biol Psychiatry, 74*(12), 898-907. doi:10.1016/j.biopsych.2013.05.036

Conradi, H. J., Ormel, J., & de Jonge, P. (2011). Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med, 41*(6), 1165-1174. doi:10.1017/S0033291710001911

Costafreda, S. G., Brammer, M. J., Vencio, R. Z., Mourao, M. L., Portela, L. A., de Castro, C. C., . . . Amaro, E., Jr. (2007). Multisite fMRI reproducibility of a motor task using identical MR systems. *J Magn Reson Imaging, 26*(4), 1122-1126. doi:10.1002/jmri.21118

Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., & Walter, H. (2010). Acute and sustained effects of cognitive emotion regulation in major depression. *Journal of Neuroscience, 30*(47), 15726-15734.

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., . . . Whiteford, H. A. (2013). Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med, 10*(11), e1001547. doi:10.1371/journal.pmed.1001547

Fox, M. D., Buckner, R. L., White, M. P., Greicius, M. D., & Pascual-Leone, A. (2012). Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biological Psychiatry, 72*(7), 595-603.

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *J Neurophysiol, 101*(6), 3270-3283. doi:10.1152/jn.90777.2008

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage, 42*(3), 1178-1184. doi:10.1016/j.neuroimage.2008.05.059

Glover, G. H. (2012). Spiral imaging in fMRI. *Neuroimage, 62*(2), 706-712. doi:10.1016/j.neuroimage.2011.10.039

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol, 21*(4), 424-430. doi:10.1097/WCO.0b013e328306f2c5

Guo, C. C., Kurth, F., Zhou, J., Mayer, E. A., Eickhoff, S. B., Kramer, J. H., & Seeley, W. W. (2012). One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. *Neuroimage, 61*(4), 1471-1483. doi:10.1016/j.neuroimage.2012.03.027

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., & Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol, 6*(7), e159. doi:10.1371/journal.pbio.0060159

Hamilton, J. P., Farmer, M., Fogelman, P., & Gotlib, I. H. (2015). Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biol Psychiatry, 78*(4), 224-230. doi:10.1016/j.biopsych.2015.02.020

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry, 23*(1), 56-62.

Hamilton, M. (1969). Diagnosis and rating of anxiety. *Br J Psychiatry, 3*, 76-79.

Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord, 134*(1-3), 20-31. doi:10.1016/j.jad.2010.11.011

Hwang, J. W., Egorova, N., Yang, X. Q., Zhang, W. Y., Chen, J., Yang, X. Y., . . . Kong, J. (2015). Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. *Transl Psychiatry, 5*, e683. doi:10.1038/tp.2015.174

Hwang, J. W., Xin, S. C., Ou, Y. M., Zhang, W. Y., Liang, Y. L., Chen, J., . . . Kong, J. (2016). Enhanced default mode network connectivity with ventral striatum in subthreshold depression individuals. *J Psychiatr Res, 76*, 111-120. doi:10.1016/j.jpsychires.2016.02.005

Jacobs, R. H., Barba, A., Gowins, J. R., Klumpp, H., Jenkins, L. M., Mickey, B. J., . . . Langenecker, S. A. (2016). Decoupling of the amygdala to other salience network regions in adolescent-onset recurrent major depressive disorder. *Psychol Med, 46*(5), 1055-1067. doi:10.1017/S0033291715002615

Jacobs, R. H., Jenkins, L. M., Gabriel, L. B., Barba, A., Ryan, K. A., Weisenbach, S. L., . . . Welsh, R. C. (2014). Increased coupling of intrinsic networks in remitted depressed youth predicts rumination and cognitive control. *PLoS One, 9*(8), e104366. doi:10.1371/journal.pone.0104366

Jenkins, L., Kassel, M., Gabriel, L., Gowins, J. R., Hymen, E., Verges, A., . . . Langenecker, S. (2016). Amygdala and dorsomedial activity during facial emotion processing in youth with remitted Major Depression.

Jo, H. J., Gotts, S. J., Reynolds, R. C., Bandettini, P. A., Martin, A., Cox, R. W., & Saad, Z. S. (2013). Effective Preprocessing Procedures Virtually Eliminate Distance-Dependent Motion Artifacts in Resting State FMRI. *J Appl Math, 2013*. doi:10.1155/2013/935154

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci, 27*(33), 8877-8884. doi:10.1523/JNEUROSCI.2063-07.2007

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry, 72*(6), 603-611. doi:10.1001/jamapsychiatry.2015.0071

Kong, X.-z., Zhen, Z., Li, X., Lu, H.-h., Wang, R., Liu, L., . . . Liu, J. (2014). Individual differences in impulsivity predict head motion during magnetic resonance imaging. *PLoS One, 9*(8), e104989.

Langenecker, S., Jenkins, L. M., Stange, J. P., Chang, Y., Deldonno, S. R., Bessette, K. L., . . . Jacobs, R. H. (under review). Integrating Multimodal Cognitive Control Measures in Prediction: Risk for Future Depressive Episodes.

Langenecker, S. A., Jacobs, R. H., & Passarotti, A. M. (2014). Current Neural and Behavioral Dimensional Constructs across Mood Disorders. *Curr Behav Neurosci Rep, 1*(3), 144-153. doi:10.1007/s40473-014-0018-x

Langenecker, S. A., Zubieta, J. K., Young, E. A., Akil, H., & Nielson, K. A. (2007). A task to manipulate attentional load, set-shifting, and inhibitory control: Convergent validity and test-retest reliability of the Parametric Go/No-Go Test. *Journal of Clinical and Experimental Neuropsychology, 29*(8), 842-853.

Liston, C., Chen, A. C., Zebley, B. D., Drysdale, A. T., Gordon, R., Leuchter, B., . . . Dubin, M. J. (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry, 76*(7), 517-526. doi:10.1016/j.biopsych.2014.01.023

Manoliu, A., Meng, C., Brandl, F., Doll, A., Tahmasian, M., Scherr, M., . . . Sorg, C. (2013). Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Front Hum Neurosci, 7*(930), 930. doi:10.3389/fnhum.2013.00930

Marchetti, I., Koster, E. H., Sonuga-Barke, E. J., & De Raedt, R. (2012). The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. *Neuropsychology review, 22*(3), 229-251.

Miller, M. B., Donovan, C. L., Van Horn, J. D., German, E., Sokol-Hessner, P., & Wolford, G. L. (2009). Unique and persistent individual patterns of brain activity across different memory retrieval tasks. *Neuroimage, 48*(3), 625-635. doi:10.1016/j.neuroimage.2009.06.033

Miller, M. B., Handy, T. C., Cutler, J., Inati, S., & Wolford, G. L. (2001). Brain activations associated with shifts in response criterion on a recognition test. *Can J Exp Psychol, 55*(2), 162-173.

Miller, M. B., Van Horn, J. D., Wolford, G. L., Handy, T. C., Valsangkar-Smyth, M., Inati, S., . . . Gazzaniga, M. S. (2002). Extensive individual differences in brain activations associated with episodic retrieval are reliable over time. *J Cogn Neurosci, 14*(8), 1200-1214. doi:10.1162/089892902760807203

Nolen-Hoeksema, S. (2001). Gender Differences in Depression. *Current Directions in Psychological Science, 10*(5), 173-176. doi:10.1111/1467-8721.00142

Nurnberger, J. I., Jr., Blehar, M. C., Kaufmann, C. A., York-Cooler, C., Simpson, S. G., Harkavy-Friedman, J., . . . Reich, T. (1994). Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch.Gen.Psychiatry, 51*(11), 849-859.

O'Connor, D., Potler, N. V., Kovacs, M., Xu, T., Ai, L., Pellman, J., . . . Ghosh, S. (2017). The Healthy Brain Network Serial Scanning Initiative: a resource for evaluating inter-individual differences and their reliabilities across scan conditions and sessions. *GigaScience, 6*(2), 1-14.

Pini, S., Cassano, G. B., Simonini, E., Savino, M., Russo, A., & Montgomery, S. A. (1997). Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. *J Affect Disord, 42*(2-3), 145-153.

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage, 59*(3), 2142-2154. doi:10.1016/j.neuroimage.2011.10.018

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage, 84*, 320-341. doi:10.1016/j.neuroimage.2013.08.048

Power, J. D., Schlaggar, B. L., & Petersen, S. E. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage, 105*, 536-551. doi:10.1016/j.neuroimage.2014.10.044

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682. doi:10.1073/pnas.98.2.676

Rao, J. A., Jenkins, L. M., Hymen, E., Feigon, M., Weisenbach, S. L., Zubieta, J. K., & Langenecker, S. A. (2016). Differential Resting State Connectivity Patterns and Impaired Semantically Cued

List Learning Test Performance in Early Course Remitted Major Depressive Disorder. *J Int Neuropsychol Soc, 22*(2), 225-239. doi:10.1017/S1355617716000011

Sambataro, F., Wolf, N. D., Pennuto, M., Vasic, N., & Wolf, R. C. (2014). Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity. *Psychol Med, 44*(10), 2041-2051. doi:10.1017/S0033291713002596

Satterthwaite, T. D., Wolf, D. H., Loughead, J., Ruparel, K., Elliott, M. A., Hakonarson, H., . . . Gur, R. E. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. *Neuroimage, 60*(1), 623-632. doi:10.1016/j.neuroimage.2011.12.063

Schallmo, M. P., Kassel, M. T., Weisenbach, S. L., Walker, S. J., Guidotti-Breting, L. M., Rao, J. A., . . . Langenecker, S. A. (2015). A new semantic list learning task to probe functioning of the Papez circuit. *J Clin Exp Neuropsychol, 37*(8), 816-833. doi:10.1080/13803395.2015.1052732

Shah, L. M., Cramer, J. A., Ferguson, M. A., Birn, R. M., & Anderson, J. S. (2016). Reliability and reproducibility of individual differences in functional connectivity acquired during task and resting state. *Brain Behav, 6*(5), e00456. doi:10.1002/brb3.456

Shehzad, Z., Kelly, A. M., Reiss, P. T., Gee, D. G., Gotimer, K., Uddin, L. Q., . . . Milham, M. P. (2009). The resting brain: unconstrained yet reliable. *Cereb Cortex, 19*(10), 2209-2229. doi:10.1093/cercor/bhn256

Shek, D. T. L., & Ma, C. (2011). Longitudinal data analyses using linear mixed models in SPSS: concepts, procedures and illustrations. *The Scientific World Journal, 11*, 42-76.

Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A, 107*(24), 11020-11025. doi:10.1073/pnas.1000446107

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*: Oxford university press.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull, 139*(1), 81-132. doi:10.1037/a0028727

Song, J., Desphande, A. S., Meier, T. B., Tudorascu, D. L., Vergun, S., Nair, V. A., . . . Prabhakaran, V. (2012). Age-related differences in test-retest reliability in resting-state brain functional connectivity. *PLoS One, 7*(12), e49847. doi:10.1371/journal.pone.0049847

Stange, J. P., Alloy, L. B., & Fresco, D. M. (2017). Inflexibility as a vulnerability to depression: A systematic qualitative review. *Clinical Psychology: Science and Practice*.

Stange, J. P., Bessette, K. L., Jenkins, L. M., Peters, A. T., Feldhaus, C., Crane, N. A., . . . Langenecker, S. A. (2017). Attenuated intrinsic connectivity within cognitive control network

among individuals with remitted depression: Temporal stability and association with negative cognitive styles. *Hum Brain Mapp*.

Tabachnick, B., & Fidell, L. (2007). *Using Multivariate Statistics*. Boston, MA: Pearson Education.

Tian, X., Wei, D., Du, X., Wang, K., Yang, J., Liu, W., . . . Qiu, J. (2016). Assessment of trait anxiety and prediction of changes in state anxiety using functional brain imaging: A test–retest study. *Neuroimage, 133*, 408-416.

Van Dijk, K. R., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage, 59*(1), 431-438. doi:10.1016/j.neuroimage.2011.07.044

Verbeke, G., & Molenberghs, G. (2009). *Linear mixed models for longitudinal data*: Springer Science & Business Media.

Wang, X., Ongur, D., Auerbach, R. P., & Yao, S. (2016). Cognitive Vulnerability to Major Depression: View from the Intrinsic Network and Cross-network Interactions. *Harv Rev Psychiatry, 24*(3), 188-201. doi:10.1097/HRP.0000000000000081

West, B. T., Galecki, A. T., & Welch, K. B. (2015). *Linear mixed models: A practical guide using statistical software* (2 ed.). Boca Raton, FL: CRC Press.

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol, 8*(1), 49-76. doi:10.1146/annurev-clinpsy-032511-143049

Wisner, K. M., Atluri, G., Lim, K. O., & Macdonald, A. W., 3rd. (2013). Neurometrics of intrinsic connectivity networks at rest using fMRI: retest reliability and cross-validation using a meta-level method. *Neuroimage, 76*, 236-251. doi:10.1016/j.neuroimage.2013.02.066

Wylie, G. R., Genova, H., DeLuca, J., Chiaravalloti, N., & Sumowski, J. F. (2014). Functional magnetic resonance imaging movers and shakers: Does subject‐movement cause sampling bias? *Hum Brain Mapp, 35*(1), 1-13.

Yan, C.-G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R. C., Di Martino, A., . . . Milham, M. P. (2013). A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage, 76*, 183-201.

Yan, C. G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R. C., Di Martino, A., . . . Milham, M. P. (2013). A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage, 76*, 183-201. doi:10.1016/j.neuroimage.2013.03.004

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., . . . Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol, 106*(3), 1125-1165. doi:10.1152/jn.00338.2011

Zeng, L. L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., . . . Hu, D. (2012). Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain, 135*(Pt 5), 1498-1507. doi:10.1093/brain/aws059

Zeng, L. L., Wang, D., Fox, M. D., Sabuncu, M., Hu, D., Ge, M., . . . Liu, H. (2014). Neurobiological basis of head motion in brain imaging. *Proc Natl Acad Sci U S A, 111*(16), 6058-6062. doi:10.1073/pnas.1317424111

Zhong, X., Pu, W., & Yao, S. (2016). Functional alterations of fronto-limbic circuit and default mode network systems in first-episode, drug-naive patients with major depressive disorder: A meta-analysis of resting-state fMRI data. *J Affect Disord, 206*, 280-286. doi:10.1016/j.jad.2016.09.005

Zhu, X., Li, R., Wang, P., & Li, J. (2014). Aberrant functional connectivity of the hippocampus in older adults with subthreshold depression. *Psych J, 3*(4), 245-253. doi:10.1002/pchj.60

Zuo, X. N., & Xing, X. X. (2014). Test-retest reliabilities of resting-state FMRI measurements in human brain functional connectomics: a systems neuroscience perspective. *Neurosci Biobehav Rev, 45*, 100-118. doi:10.1016/j.neubiorev.2014.05.009

VITA

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Education

University of Illinois at Chicago; Chicago, IL — 2015 - present
Master of Arts in Clinical Psychology – expected July 2017
Clinical Psychology Doctoral Program
Advisor: Scott A Langenecker, Ph.D.

Boston College; Chestnut Hill, MA — 2007 - 2011
Bachelor of Arts in Psychology, cum laude
Clinical Psychology Concentration

Grants and Fellowships

$8,000	Undergraduate Research Fellowship (Boston College)	2010
$2,000	Undergraduate Research Fellowship (Boston College)	2009

Honors and Awards

UIC Psychology Department Travel Award ($600)	2017
Phi Kappa Phi (UIC)	2016
Nomination for 2016 Top Poster Award at SOBP 71st Annual Meeting	2016
Dean's List (Boston College)	2007- 2011
Departmental Psychology Honors (Boston College)	2011
A&S Honors (Boston College)	2011
Psi Chi (Boston College)	2010

Research Experience

Neuropsychology Technician — 2017 - present
Neuropsychiatric Institute, MATRICS study
University of Illinois at Chicago, IL
Supervisor: Cherise Rosen, Ph.D.
Conduct and score neuropsychological assessments with adults with first-episode schizophrenia.

Independent Evaluator/Technician — 2016 – present
Pediatric Mood Disorders Clinic
University of Illinois at Chicago, IL

Supervisors: Amy E. West, Ph.D. & Amy T. Peters, M.A.
Conduct semi-structured clinical intakes and neuropsychological assessments with adolescents enrolled in a study evaluating inflammatory and neurocognitive markers in mood pathology.

Graduate Research Assistant 2015 - present
Cognitive Neuroscience Center, MEND2 Lab
University of Illinois at Chicago, IL
Center Director: Scott A. Langenecker, Ph.D.
Program, preprocess and functional MRI data for manuscripts and grant submissions. Conduct clinical interviews with adults in studies on mood disorders.

Clinical Research Assistant 2011 –2015
Olin Neuropsychiatry Research Center;
Institute of Living/Hartford Hospital, Hartford, CT
Center Director: Godfrey D. Pearlson, M.D.
Clinical Neuroscience and Development Lab
Lab Director: Michael C. Stevens, Ph.D.
Conducted semi-structured diagnostic interviews, mood, attention and neuropsychological assessments. Created and administered Standard Operation Procedures Manual for neuronavigation and rTMS procedures. Responsible for study recruitment, IRB correspondence, funding agency correspondence, data management and clinical research assessment. Designed, programmed, preprocessed and analyzed behavioral, neuropsychological, functional and structural MRI data. Co-designed and validated aggressive impulsivity questionnaire for study use. Trained new research staff and volunteers. Coordinated and administered protocols for research, pilot and treatment studies in adolescent psychiatric disorders:

- *Neural Architecture of Emotion Regulation, Adolescent Development and Depression (R01MH102854)*
- *rTMS Treatment for Adolescents with Depression (Internal Donor)*
- *Characterizing Two Distinct ADHD Neurobiologies with fMRI (RO1MH080956-05)*
- *Effects of Working Memory Training on ADHD Brain Dysfunction (R21HD061915-01A1)*
- *Impulsivity and Suicidal Depression in Adolescents*
- *Neuropsychiatric Changes After Sports Concussions in Adolescents*
- *Persistent Working Memory Difficulties in TBI: Treatment with tDCS*

Thesis Student/Research Assistant 2010 – 2011
Interdisciplinary Affective Science Laboratory
Northeastern University; Boston, MA
Director: Lisa Feldman Barrett, Ph.D.
Direct Supervisor: Jennifer M. B. Fugate, Ph.D.
Thesis: "Examining Looking Patterns of Facial Depictions of Emotion"
Designed, administered, coded and analyzed behavioral paradigm for eye-tracking study. Responsible for 2 university IRB correspondences, study recruitment, data management, training, and preparation of findings for conferences and manuscripts.

Research Assistant 2009 – 2010
Interdisciplinary Affective Science Laboratory
Boston College; Chestnut Hill, MA
Director: Lisa Feldman Barrett, Ph.D.
Direct Supervisors: Jennifer M. B. Fugate, Ph.D. & Maria Gendron, Ph.D.
"Language and the Perception of Emotion" – *NSF BCS 0721260*
Programmed and analyzed behavioral emotion categorization paradigms. Responsible for study recruitment, IRB correspondence, task administration with young adults, and preparation of findings for conferences and manuscripts.

Clinical Experience

Clinician 2015 - present
Office of Applied Psychological Services
University of Illinois at Chicago, IL
Supervisors: Amanda Lorenz, Ph.D., Bibiana Adames, Ph.D., & Jenna Rowen, Ph.D.
Conduct semi-structured clinical interviews, neuropsychological tests, and administer evidence-based psychotherapy interventions.

TMS Technician 2013 – 2014
Institute of Living, Hartford Hospital
Hartford, CT
Supervisor: John W. Goethe, M.D.
Administered rTMS treatment using NeuroStar equipment to patients with MDD or GAD.

Rape Crisis Hotline Counselor 2012 – 2013
Connecticut Sexual Advocacy Crisis Services, YWCA
New Britain, CT
Supervisor: Kristen N Gienty, M.A.
Counseled clients in crisis by phone; offered services, advocacy and support to clients and families at hospitals, police stations, and court rooms.

Neurofeedback Assistant 2011
The NeuroDevelopment Center
Providence, RI
Supervisors: Laurence M Hirshberg, Ph.D. & Kyle D. Frederick, M.S.
Developed social skills curriculum for adolescents with Asperger's syndrome; scored psychological testing and assisted administration of neurofeedback EEG with depressed patients

Group Therapy Co-Leader 2011
Children's Hospital Boston Inpatient Psychiatric Unit
Boston, MA
Supervisors: Ariel Botta, M.S.W., & Jessica Kimball, CTRS
Co-led group psychotherapy with actively suicidal adolescents; conducted milieu therapy, group assertiveness training, patient education, relaxation and cognitive therapy sessions.

Preventative Mental Health Coordinator 2010
Cambridge Center for Families
Cambridge, MA

Supervisor: Beverly Halpern, M.A.
Disseminated and administered preventative mental health initiatives for young children through educational groups and town fairs.

Teaching Experience

Teaching Assistant 2016 - present
Psychology Department, University of Illinois at Chicago
- Introduction to Psychology
- Personality Theories
- Fieldwork in Applied Psychology
- Statistics

Peer-Reviewed Publications

Stange, JP, **Bessette, KL**, Jenkins, LM, Peters, AT, Feldhaus, C, Crane, NA, Ajilore, O, Jacobs, RH, Watkins, ER, & Langenecker, SA (2017). Attenuated intrinsic connectivity within cognitive control network among individuals with remitted depression: Temporal stability and association with negative cognitive styles. *Human Brain Mapping, 38*(6), 2939-2954. doi: 10.1002/hbm.23564.

Fradkin, Y, Khadka, S, **Bessette, KL,** & Stevens, MC (2016). The relationship of impulsivity and cortical thickness in depressed and non-depressed adolescents. *Brain imaging and behavior*, 1-11. doi:10.1007/s11682-016-9612-8.

Ruf, BM, **Bessette, KL**, Pearlson, GD, & Stevens, MC (2016). Effect of trait anxiety on cognitive test performance in adolescents with and without attention-deficit/hyperactivity disorder. *Journal of Clinical and Experimental Neuropsychology*, *39*(5), 1-15. doi:10.1080/13803395.2016.1232373.

Khadka, S, Pearlson, GD, Calhoun, VD, Liu, J, Gelernter, J, **Bessette, KL**, & Stevens, MC (2016). Multivariate imaging genetics study of MRI gray matter volume and SNPs reveals biological pathways correlated with brain structural differences in Attention Deficit Hyperactivity Disorder. *Frontiers in Psychiatry, 7,* 128. doi:10.3389/fpsyt.2016.00128.

Stevens, MC, Gaynor, A, **Bessette, KL**, & Pearlson, GD (2015). A preliminary study of the effects of working memory training on brain function. *Brain imaging and behavior, 10*(2), 387-407. doi:10.1007/s11682-015-9416-2.

Bessette, KL, Nave, AM, Caprihan, A, & Stevens, MC (2014). White Matter Abnormalities in Adolescents with Major Depressive Disorder. *Brain imaging and behavior, 8*(4), 531-541. doi:10.1007/s11682-013-9274-8.

Publications Under Review

Stange, JP, Jenkins, LM, **Bessette, KL,** Kling, LR, Hamlat, EJ, DelDonno, SR, Luan Phan, K, Passarotti, AM, Ajilore, O, & Langenecker, SA (under review). Predictors of attrition in longitudinal neuroimaging research: Inhibitory control, head movement, and resting-state functional connectivity.

Stange, JP, Jenkins, LM, Hamlat, EJ, **Bessette, KL,** DelDonno, SR, Kling, LR, Passarotti, AM, Luan Phan, K, Klumpp, H, Ryan, KA & Langenecker, SA (under review). Disrupted engagement of networks supporting hot and cold cognition in remitted major depressive disorder.

Jenkins, LM, Stange, JP, **Bessette, KL,** Chang, Y, Corwin, SD, Skerrett, KA, Patron, VG, Zubieta, J, Crane, NA, Passarotti, A, Pine, DS, & Langenecker, SA (under review). Differential engagement of cognitive control regions and subgenual cingulate based upon presence or absence of comorbid anxiety with depression.

Langenecker, SA, Jenkins, LM, Stange, JP, Chang, Y, DelDonno, SR, **Bessette, KL,** Passarotti, AM, Bhaumik, RM, Ajilore, O & Jacobs, RH (under review). Cognitive control inefficiencies reliably predict recurrence of depressive episodes: A precision medicine example.

Bessette, KL, Jenkins, LM, Skerrett, KA, Gowins, JR, DelDonno, SR, Zubieta, J, McInnis, MG, Jacobs, RH, Ajilore, O, & Langenecker, SA (under review). Enhanced between- and diminished within-network connectivity of default mode seeds in early adult Major Depressive Disorder: reproducibility and endophenotypic correlations.

Stevens, MC, Pearlson, GD, Calhoun, VD, & **Bessette, KL** (under review). Functional neuroimaging evidence for distinct neurobiological pathways in Attention-Deficit/Hyperactivity Disorder.

Talk Presentations

Bessette, KL, et al. (2017). *Aberrant Default Network Connectivity as an Endophenotype of Depression.* Data blitz talk presented at UIC 3rd Annual Cross Program Conference, Chicago, IL.

Bessette, KL, et al. (2016). *Cognitive Vulnerabilities for Depression and Alcohol Use*. Talk presented at UIC Center for Alcohol Research in Epigenetics Neuroscience Seminar Series, Chicago, IL.

Conference Presentations

Bessette, KL, et al. (2017). *Hyperconnectivity within the Cognitive Control Network Predicts Depressive Relapse among Adolescents*. Poster presented at Society of Biological Psychiatry 72nd Annual Scientific Program and Convention, San Diego, CA.

Peters, AT, Jenkins, LM, Stange, JP, **Bessette, KL**, Skerrett, KA, Kling, LR & Langenecker, SA (2017). *Acute cortisol reactivity is associated with increased connectivity from default mode to cognitive control networks in remitted adolescent-onset depression*. Poster presented at Society of Biological Psychiatry 72nd Annual Scientific Program and Convention, San Diego, CA.

Ajilore, O, Jacobs, RH, **Bessette, KL**, Feldhaus, C, Barba, A, Jenkins, LM, Leow, A, & Langenecker, SA. (2017) *Altered dynamic brain network modularity in adolescent remitted depression*. Poster presented at Network Neuroscience Satellite Site for NetSci2017 Conference, Indianapolis, IN.

Bessette, KL, et al. (2017). *Comorbid Depression and Anxiety Has Greater Top-Down and Bottom-Up Neural Emotional Processing than Depression Alone in the Remitted State*. Poster presented at International Neuropsychological Society 45th Annual Meeting, New Orleans, LA.

Kling, LR, **Bessette, KL**, Skerrett, KA, Phillips, ML, & Langenecker, SA (2017). *Cluster Analysis-Defined Symptom Subtypes and Life Event and Neuropsychological Correlates in remitted Major Depressive Disorder.* Poster presented at International Neuropsychological Society 45th Annual Meeting, New Orleans, LA.

Stange, JP, **Bessette, KL**, Jenkins, LM, Burkhouse, KL, Peters, AT, Feldhaus, C, Crane, NA,

Ajilore, O, Jacobs, RH, Watkins, ER, & Langenecker, SA (2016). *Attenuated Intrinsic Connectivity within the Cognitive Control Network Among Individuals with Remitted Depression is Associated with Cognitive Control Deficits and Negative Cognitive Styles.* Poster presented at the 2016 Federation of European Neuroscience Societies Brain Conference on New Insights into Psychiatric Disorders through Computational, Developmental and Biological Approaches, Copenhagen, Denmark.

Stange, JP, **Bessette, KL**, Jenkins, LM, Burkhouse, KL, Peters, AT, Feldhaus, C, Crane, NA, Ajilore, O, Jacobs, RH, Watkins, ER, & Langenecker, SA (2016). *Attenuated Intrinsic Connectivity within the Cognitive Control Network Among Individuals with Remitted Depression is Associated with Cognitive Control Deficits and Negative Cognitive Styles.* Poster presented at the 2016 National Network of Depression Centers, Denver, CO.

Bessette, KL, Stange, JP, Burkhouse, KL, Skerrett, KA, Jacobs, RH, & Langenecker, SA (2016). *Negative Thought Patterns Predict Past Depression and Current and Future Functioning.* Poster session at UIC 7th Annual Department of Psychiatry Research Forum, Chicago, IL.

Bessette, KL, Jenkins, LM, Barba, A, Jacobs, RH, Skerrett, KA & Langenecker, SA (2016). *Stable Left PCC to Right DLPFC Hyperconnectivity in Remitted Depressed Young Adults.* Poster session at UIC 7th Annual Department of Psychiatry Research Forum, Chicago, IL.

Bessette, KL, Stange, JP, Burkhouse, KL, Skerrett, KA, Jacobs, RH, & Langenecker, SA (2016). *Negative Thought Patterns Predict Past Depression and Current and Future Functioning.* Poster presented at 28th Association for Psychological Science Annual Convention, Chicago, IL.

Bessette, KL, Jenkins, LM, Barba, A, Jacobs, RH, Skerrett, KA & Langenecker, SA (2016). *Stable Left PCC to Right DLPFC Hyperconnectivity in Young Adults with a History of Depression*. Poster presented at the Society for Biological Psychiatry 71st Annual Scientific Meeting, Atlanta, GA.

Bessette, KL, Pearlson, GD, & Stevens, MC (2015). *Associations of Fractional Anisotropy and Neuropsychological Dysfunction in AD/HD and non-AD/HD Youth*. Poster presented at the Society for Biological Psychiatry 70th Annual Scientific Meeting, Atlanta, GA.

Fradkin, Y, Stevens, MC, Khadka, S, **Bessette, KL** (2014). *Relationship of Impulsivity and Cortical Surface Area in Depressed and Non-Depressed Adolescents.* Poster session presented at the American Academy of Child & Adolescent Psychiatry 61st Annual Meeting, San Diego, CA.

Ruf, B, **Bessette, KL,** Pearlson, GD, Stevens MC (2014). *Effect of trait anxiety on cognitive test performance in adolescents with and without ADHD.* Poster presented at University of Connecticut Health Center Psychiatry Research Bonanza, Hartford, CT.

Khadka, S, **Bessette, KL,** Gaynor, A, Pearlson, GD, Witt, ST, Stevens, MC (2013). *Effective connectivity during voluntary cognitive re-appraisal emotion regulation.* Poster presented at the 19th Annual Meeting of the Organization for Human Brain Mapping, Seattle, WA.

von Pechmann, DF, **Bessette, KL,** Stevens, MC, Shane, MS (2013). *Neuromodulation of Response Inhibition in AD/HD.* Poster session presented at the Society for Biological Psychiatry 68th Annual Scientific Meeting, San Francisco, CA.

Khadka, S, Witt, ST, Gaynor, A, **Bessette, KL,** Stevens, MC (2013). *Neural Architecture of Voluntary Cognitive Re-Appraisal and Emotion Regulation.* Poster session presented at the Society for Biological Psychiatry 68th Annual Scientific Meeting, San Francisco, CA.

Gaynor, A, Whitman, J, **Bessette, K,** Stevens, MC (2013). *Effects of Intensive Working Memory Treatment on Brain Activity in Adolescent Combined-Subtype ADHD.* Poster session presented at the Society for Biological Psychiatry 68th Annual Scientific Meeting, San Francisco, CA.

Fugate, JMB, Gendron, M, **Bessette, KL**, & Barrett, LF (2012). *Affect Primarily Drives Looking Pattern Differences to Emotion Faces.* Poster session presented at the Society for Personality and Social Psychology Conference, San Diego, CA.

Bessette, KL, Fugate, JMB, Gendron, M, & Barrett, LF (2011). *Examining Looking Patterns of Affective Faces without Context.* Poster session presented at the Boston College Undergraduate Research Conference, Chestnut Hill, MA.

Fugate, JMB, **Bessette, K,** & Barrett, LF (2010). *Explicitly and Implicitly Primed Emotion Words Affect Perceptual Emotion Judgments.* Poster session presented at the Association for Psychological Science Conference, Boston, MA.

Fugate, JMB, **Bessette, K,** & Barrett, LF (2010). *Explicitly and Implicitly Primed Words Affect Perceptual Emotion Judgments.* Poster session presented at the Boston College Undergraduate Research Conference, Chestnut Hill, MA.

Fugate, JMB, **Bessette, K,** & Barrett, LF (2010). *Explicitly and implicitly primed emotion words affect perceptual judgments of emotion.* Poster session presented at the Emotion Preconference for the Society for Personality and Social Psychology Conference, Las Vegas, NE.

Certifications

American Red Cross Adult & Child CPR Certification	2003 – 2015
Risky Connections Crisis Training Certification	2015
Duke TMS Fellowship Certification	2013
NeuroStar Transcranial Magnetic Stimulation Device, licensed operator	2013
Soterix tDCS Certification at Burke Rehabilitation Hospital	2013
Rape Crisis Counseling Certification	2013

Professional Affiliations

International Neuropsychological Society	2017
Society for a Science of Clinical Psychology	2016 - Present
Society of Biological Psychiatry	2013 – Present
Association for Psychological Science	2009 – Present
Society for Personality and Social Psychology	2009 – 2014

Skills

Proficiency in:

C++, Linux/Unix
E-Basic
E-Prime 2.0 Application Suite
NITRC Conn Toolbox
SPSS (PASW) statistical software
R Statistical Software
Microsoft Office Suite 2016
SPM8, FSL 5.0
MatLab 8.0
Gift Toolbox (GICA)
TBSS (Tract-based Spatial Statistics)
Adobe Photoshop, Illustrator
NVU, FantaMorph