10-1-2020

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This is the peer reviewed version of the following article: [Makowski, C., Lewis, J.D., Khundrakpam, B., Tardif, C.L., Palaniyappan, L., Joober, R., Malla, A., Shah, J.L., Bodnar, M., Chakravarty, M.M., et al. (2020). Altered Hippocampal Centrality and Dynamic Anatomical Covariance of Intracortical Microstructure in First Episode Psychosis." Hippocampus, vol. 30, no. 10, June 2020, pp. 1058–72, https://doi.org/10.1002/hipo.23215.

Altered hippocampal centrality and Dynamic Anatomical Covariance of intracortical microstructure in First Episode Psychosis

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Running Title: Altered Hippocampal Centrality in Psychosis
Word Count: Abstract: 229, Text: 5333
Figures: 4. **Tables**: 1. **Supplementary Information:** 1.
Keywords: white matter, limbic structure, participation coefficient, negative symptoms, verbal memory, psychosis

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centrality and dynamic anatomical covariance of intracortical microstructure in first episode psychosis. Hippocampus, 30(10). DOI: 10.1002/hipo.23215

ABSTRACT

Background. Hippocampal circuitry has been posited to be fundamental to positive symptoms in psychosis, but its contributions to other factors important for outcome remains unclear. We hypothesized that longitudinal changes in the hippocampal circuit and concomitant changes of intracortical microstructure are altered in first episode psychosis (FEP) patients and that such changes are associated with negative symptoms and verbal memory.

Methods. Longitudinal brain scans (2-4 visits over 3-15 months) were acquired for 27 FEP and 29 age- and sex-matched healthy controls. Quantitative T1 maps, sensitive to myelin content, were used to sample the microstructure of the hippocampal subfields and output circuitry (fimbria, alveus, fornix, mammillary bodies), and intracortical regions. Dynamic anatomical covariance in pair-wise regional trajectories were assessed for each subject, and graph theory was used to calculate a participation coefficient metric that quantifies the similarity/divergence between hippocampal and intracortical microstructure.

Results. The mean participation coefficient of the hippocampus was significantly reduced in FEP patients compared to controls, reflecting differences in output hippocampal regions. Importantly, lower participation coefficient of the hippocampal circuit was associated with worse negative symptoms, a relationship that was mediated by changes in verbal memory.

Conclusions. This study provides evidence for reduced hippocampal centrality in FEP and concomitant changes in intracortical anatomy. Myelin-rich output regions of the hippocampus may be an important biological trigger in early psychosis, with cascading effects on broader cortical networks and resultant clinical profiles.

INTRODUCTION

The hippocampus and associated circuitry have long been implicated in the emergence of psychosis (Lieberman et al., 2018; Tamminga, Southcott, Sacco, Wagner, & Ghose, 2012; Tamminga, Stan, & Wagner, 2010). Evidence suggests that the hippocampus is positioned as a key convergence zone for cortical regions (Mišić, Goñi, Betzel, Sporns, & McIntosh, 2014). A better understanding of the role of the hippocampus within broader neocortical networks in psychosis may shed light on the highly replicated finding and robust effect size of hippocampal structural abnormalities across the psychosis spectrum (Harrison, 2004; Hibar et al., 2016; Mathew et al., 2014; Narr et al., 2004; van Erp et al., 2016).

Beyond positive symptoms, dense hippocampal connections to other cortical regions suggest a role for the hippocampus in the manifestation of other functionally important clinical symptoms lacking effective treatment in early psychosis, namely verbal memory deficits and negative symptoms (Hovington, Bodnar, Joober, Malla, & Lepage, 2013; Jordan et al., 2014). Importantly, the hippocampus has been shown to be a hub region for accurate memory retrieval in healthy individuals (Schedlbauer, Copara, Watrous, & Ekstrom, 2014), further justifying the need to focus on the centrality of the hippocampus in memory deficits and associated symptoms in psychosis. Cross-sectional associations between negative symptoms and verbal memory in first episode of psychosis (FEP) patients (Cirillo & Seidman, 2003; Makowski, Lewis, Lepage, Malla, Joober, Evans, et al., 2019) have been shown, but the dynamic relationship between the two remains unclear. Several authors propose a model in psychotic disorders where impaired cognition, including verbal memory deficits, give rise to negative symptoms and contribute to a patient's functional outcome (Foussias, Agid, Fervaha, & Remington, 2014; Jordan et al., 2014).

The presentation of negative symptoms and verbal memory deficits may be subserved by

the connections of the hippocampus to the cortex both proximally, i.e. medial temporal lobe (Bird & Burgess, 2008), and more distally, i.e. prefrontal cortex (Godsil, Kiss, Spedding, & Jay, 2013). Corroborating this, relationships between negative symptoms and hippocampal-cortical anatomy have previously been reported (Bernasconi et al., 2015; Takayanagi et al., 2013). Investigating the microstructure of neocortical regions and fine-grained structures of the hippocampal subfields may elucidate these mechanisms. Recent MRI advances have allowed for quantitative *in vivo* measurement of such meso-structures (Amaral et al., 2018; Baglivo et al., 2017; Ho et al., 2017; Pipitone et al., 2014; Tardif et al., 2018), offering an unprecedented opportunity to investigate the contribution of individual hippocampal components that may be dysfunctional around psychosis onset. Intracortical myelin is also of interest; the majority of white matter fibers are found intracortically (Schüz & Braitenburg, 2002) and these fibers are particularly amenable to experience-dependent plasticity and illness-related alterations (Bartzokis, 2004).

Graph theory approaches capture summary metrics of the interaction between brain regions, i.e. the connectome, and offer a novel perspective on brain organization in psychosis (Palaniyappan et al., 2016; Rubinov & Sporns, 2010; van den Heuvel, Mandl, Stam, Kahn, & Hulshoff Pol, 2010). A recent study found that schizophrenia patients had significantly more sparse, or less modular, organization of the hippocampus compared to healthy controls, and this was related to relational memory function (Avery, Rogers, & Heckers, 2018). However, there is a need to incorporate longitudinal neuroimaging data in the early phases of psychosis (Collin & Keshavan, 2018).

Our previous work in FEP described changes in cortical white-gray matter contrast, a putative marker of peri-cortical myelin, associated with verbal memory deficits and negative symptoms (Makowski, Lewis, Lepage, Malla, Joober, Evans, et al., 2019; Makowski, Lewis,

Lepage, Malla, Joober, Lepage, et al., 2019). We aimed to bridge these findings and better understand the similarity or divergence in hippocampal microstructure to cortical anatomy. We adapted our previous work on cortical maturational coupling (Khundrakpam et al., 2017), which is based on principles of anatomical covariance (Evans, 2013), to investigate whether dynamic anatomical covariance (DAC) between the hippocampal circuit and the cortex was altered in FEP patients. We use a graph measure of centrality, the participation coefficient (Rubinov & Sporns, 2010), to assess DAC between hippocampal and intracortical microstructure. We hypothesize that patients will have reduced coupling between hippocampal circuit and cortex, particularly driven by output hippocampal substructures, e.g. CA1 and fornix. At the behavioural level, we aimed to extend previous cross-sectional findings and better elucidate the dynamic relationship between negative symptoms and verbal memory deficits shortly after a FEP. We hypothesize that hippocampal centrality will act as a mediator between verbal memory deficits and negative symptom severity. This would offer a meaningful biological mechanism for the proposed framework of cognitive deficits that influence negative symptoms.

METHODS

Subjects. Patients were recruited from the Prevention and Early Intervention Program for Psychosis (PEPP-Montréal) (Iyer, Jordan, MacDonald, Joober, & Malla, 2015) at the Douglas Institute in Montreal, Canada, and were part of an ongoing longitudinal naturalistic outcome study. Inclusion criteria at PEPP include a diagnosis of non-affective (e.g. schizophrenia, schizoaffective) and affective (e.g. bipolar, depression with psychotic features) psychosis, IQ>70, and limited (maximum 1 month) to no previous exposure to antipsychotic medication. Diagnosis was made with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-

Patient Edition. PEPP-Montreal has previously observed in a large sample of over 200 patients that 76% of patients retain their initial diagnosis at one-year follow-up (Pope, Joober, & Malla, 2013). Antipsychotic medication exposure for each patient was recorded as chlorpromazine equivalents, taking into account medication adherence. Medication adherence [0=never (0%), 1=very infrequently (1% to 25%), 2=sometimes (26% to 50%), 3=quite often (51% to 75%), 4=fully (76% to 100%)] was determined using a validated protocol based on composite information obtained from the patient, family members, and treating team and has been shown by our group previously to be as efficacious as pill-counting (Cassidy et al. 2010).

Patients recruited to PEPP (ages 18-35) were invited to take part in a neuroimaging study, comprising four timepoints (baseline, 3/9/15-month follow-ups), with clinical and cognitive data collected concurrently. Age-matched healthy controls were recruited within the same catchment area under the same four-timepoint protocol. All participants provided written informed consent, and the research protocol was approved by the Human Ethics Review Board at the Douglas Institute. Twenty-seven patients (Female, N=9) and 29 healthy controls (Female, N=13) with at least two usable scans were enrolled.

Negative symptoms and verbal memory data. The relationship between negative symptoms and verbal memory was assessed longitudinally. Two patients were missing clinical/cognitive data. Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (N. Andreasen, 1984), with good inter-rater reliability (κ=0.71) at PEPP-Montreal (Jordan et al., 2018). Item-level scores, excluding the Attention subdomain which has been shown to poorly cluster with other negative symptoms (Malla et al., 2002; Peralta & Cuesta, 1999), were summed for each patient per timepoint. To assess rate of change in symptoms over time, a linear

model was fit to each subject's longitudinal SANS data, where the slope represented a single metric of symptom change over time. Verbal memory was assessed for both FEP patients and healthy controls with the Logical Memory subtests of the Wechsler Memory Scale–Fourth Edition (WMS-IV) (Weschler, 2009). Scaled scores for immediate recall (Logical Memory I) and delayed recall (Logical Memory II) were averaged to obtain a global score of memory recall performance. As with negative symptoms, a single longitudinal score was derived for each participant, by calculating the rate of change in verbal memory performance.

MRI acquisition. Participants underwent MRI scanning on a 3T Siemens Magnetom Trio scanner at the Douglas Institute. Anatomical MRI acquisition was comprised of a T1-weighted MPRAGE sequence (repetition time[TR]=2300ms, echo time[TE]=2.98ms, field of view[FOV]=256mm, voxel size=1mm^3, 192 slices, flip angle=9°, scan time ~5 minutes), a high-resolution T2-weighted image to capture detailed hippocampal subfield information (TR=2500ms, TE=198ms, FOV=206mm, voxel size=0.64mm^3, 320 slices, scan time ~10 minutes), and an MP2RAGE sequence[37], which includes a quantitative T1 (qT1) map, serving as a proxy measure of myelin content (TR=5000ms, TE=2.01ms, first T1=700ms, second T1=2500mm, first flip angle=4°, second flip angle=5°, FOV 256mm, voxel size 1mm^3, 176 slices, scan time ~9 minutes). The MP2RAGE acquisition combines two different images acquired with slightly different inversion times, to diminish the spatial inhomogeneities typically caused by the transmit B_1 field, and allows for quantification of bias-free T1 relaxation times (Marques et al., 2010). Test-retest reliability of the MP2RAGE sequence is very high, with a recent study reporting a reliability of r^2=0.94 (Metere, Kober, Möller, & Schäfer, 2017). Slight deviations to the MP2RAGE protocol were acquired in a subset of the scans (see Supplementary Methods).

MRI processing.

Figure 1 summarizes the image processing and analysis workflow, described below.

Hippocampal labels. T2-weighted images were submitted to the Multiple Automatically Generated Templates (MAGeT)-Brain algorithm (https://github.com/CobraLab/MAGeTbrain) (Chakravarty et al., 2013; Pipitone et al., 2014) to extract 9 structures per hemisphere: the hippocampal subfields (cornu ammonis[CA]1, CA2/3, CA4/dentate gyrus[DG], subiculum, and molecular layer) (Winterburn et al., 2013) and surrounding white matter structures (alveus, fimbria, fornix, mammillary bodies) (Amaral et al., 2018). See Supplementary Methods for image pre/post-processing.

Sampling of the qT1 map for hippocampal labels. T2-weighted images were affinely registered to MP2RAGE UNI scans ($1mm^3$), and the transforms were applied to the hippocampal labels. Mean qT1 values for each hippocampal subfield and white matter label were then sampled for each participant from the MP2RAGE qT1 map (**Figure 1**-Step 1).

Generation of Cortical Surfaces. Raw T1-weighted images were submitted to the CIVET pipeline (Version 2.1.0: http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET) for extraction of gray and white matter surfaces, described previously (June et al., 2005; Lewis, Evans, & Tohka, 2018; Makowski, Lewis, Lepage, Malla, Joober, Lepage, et al., 2019). A distance map relative to the white surface provided by CIVET was created at 0.25x0.25x0.25mm resolution, smoothed with a 0.5mm FWHM Gaussian kernel, and used to create a gradient vector field of the distance map (Lewis et al., 2018). Down-sampling and smoothing was done prior to creation of the vector field, due to the fact that at low resolution, some regions (particularly at the tips of gyri) have very thin

white matter. From here, four additional surfaces were generated at 35-45-55-65% cortical depths between the pial and white matter surfaces, comprising intracortical surfaces. Surfaces <35% or >65% cortical depths were not considered to avoid partial volume effects (Nürnberger et al., 2017).

Sampling of qT1 maps for intracortical surfaces. The MP2RAGE qT1 map was registered to stereotaxic space and upsampled to 0.5x0.5x0.5mm. The qT1 map was sampled along 81,924 vertices for the intracortical surfaces (**Figure 1**-Step 1). The resulting surface maps were smoothed with a 20mm FWHM Gaussian kernel and qT1 values at linked vertices across the four intracortical depths were averaged to mitigate the effects of noise, yielding one value per vertex to summarize intracortical microstructure. See Supplementary Methods for quality control procedures.

Dynamic Anatomical Covariance (DAC). The Desikan Killiany-Tourville (DKT) atlas was used to parcellate the brain into 62 regions (Klein & Tourville, 2012). DKT regions are listed in Supplementary Table 1 and shown in **Figure 1**-Step 2. Subject-specific DAC matrices were created, based on methods in (Khundrakpam et al., 2017). To create these matrices, the theta (θ) angle of separation was calculated between the qT1 rates of change of any two brain regions between each pair of timepoints. The cosine of the θ angle was calculated to normalize values between 0 and 1. For participants with more than one consecutive pair of timepoints, the cosines of the pair-wise θ angles were multiplied. Thus, subject-specific matrices reflected the coordinated change between all possible pairs of regions, based on pairwise cosine similarity values derived from the slopes of linear changes in qT1 in an 80x80 matrix. A cumulative distribution function

(CDF) kernel was applied to enhance the contrast between real and spurious links for each matrix, as described in (Khundrakpam et al., 2017) (**Figure 1**-Step 3).

Graph theory application: Participation Coefficient of hippocampal module. To determine whether the hippocampal circuit has altered centrality in relation to other cortical modules in FEP, we labeled the 62 DKT regions into 7 functional networks based on (Yeo et al., 2011). It has been shown that these 7 functional networks show high modularity and provide a strong fit to structural connectivity data (Baum et al., 2017). Hippocampal subfields and output white matter defined a separate module. See Supplementary Figure 1 for visualization of node assignment. The Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) was used to calculate the participation coefficient (PC) of each module (Rubinov & Sporns, 2010). The PC reflects the distribution of co-occurring changes between a particular set of nodes in a given module and nodes of other modules, i.e. a node with a high PC suggests that node has higher between-module than within-module covariance. See **Figure 1**-Step 4. A PC was derived for each of the 80 nodes, as well as an average PC for each of the modules.

See Box 1 for a summary of key neuroimaging and graph theory terms used in this paper. We also provide readers with key references for these terms that provide more in-depth information and reviews on the included metrics.

Box 1.

Dynamic Anatomical Covariance (DAC): cosine similarity of longitudinal changes in qT1 values between pairs of regions. Indices are obtained for each possible pair of regions to form a subject-specific matrix of co-occurring change. Please see the "maturational coupling" method presented in Khundrakpam et al., (2017) and a review of anatomical covariance methods in Evans (2013).

Hippocampal centrality: participation coefficient based on the cosine similarity of longitudinal changes in qT1 values

Hippocampal module: a module comprising 9 regions per hemisphere of the hippocampal-white matter circuit (i.e. CA1, CA2/3, CA4/DG, subiculum, molecular layer, alveus, fimbria, fornix, mammillary bodies). Please see Amaral et al., (2018) for details on the anatomical atlas of regions used in this hippocampal module.

Module: a community of brain regions within a graph, defined *a priori* in this study (Rubinov & Sporns 2010).

Neocortical modules: 7 non-overlapping modules comprising regions within the following networks: limbic, frontoparietal control, default mode, somatomotor, dorsal attention, ventral attention, and visual (Yeo et al., 2011).

Node: a brain region within a graph (Rubinov & Sporns 2010).

Participation Coefficient (PC): a graph measure reflecting the distribution of co-occurring changes between a particular set of nodes in a given module and nodes of other modules

Statistical analyses. Demographic and clinical variables were analysed with independent sample t-tests and Mann-Whitney U tests for normally and non-normally distributed data, respectively. We tested for associations between rates of change in negative symptoms and logical memory scores in FEP patients with Pearson correlation coefficients. Analyses of behavioural and clinical variables were conducted using PASW Statistics 21 (SPSS inc., 2009, Chicago, IL, USA) and were two-tailed with a critical *p*-value of 0.05.

Group differences in DAC. The mean of subject-specific DAC matrices were derived for FEP and

healthy controls separately to assess whether there were group differences in coordinated coupling of qT1 values across hippocampal-intracortical regions. DAC matrices were compared between groups by converting coupling metrics (i.e. the cosine similarity score) to z-scores using a Fisher transformation and comparing the differences to a normal distribution to obtain p-values. P-values were thresholded using a two-stage false discovery rate (FDR) correction, which limits the false-positive rate for a family of hypothesis tests below 0.05 (Benjamini, Krieger, & Yekutieli, 2006). Only the lower triangle of the thresholded matrices (i.e. non-duplicate pairs of regions, yielding a total of 3160 [80x79/2] tests) were considered. Results were visualized with BrainNet Viewer (M. Xia, Wang, & He, 2013). Supplementary analyses were conducted to assess group differences in qT1 values of the hippocampal circuit and vertex-wise IC microstructure.

Group differences in hippocampal PC. Mean PC values across hippocampal module nodes were derived per subject, adjusted for age and sex. Group differences were assessed with an independent sample t-test. Post-hoc tests were conducted to identify the hippocampal subregion that contributed to significant group differences.

Testing centrality of cortical modules. To ensure our results were specific to centrality of the hippocampal module, the same analyses were conducted testing group differences in PC and relationships with changes in verbal memory/negative symptoms of all cortical modules.

Relationship between negative symptoms and verbal memory deficits. The interaction of changes in negative symptoms and verbal memory on mean hippocampal PC was tested, contingent on whether results were significant in the behavioural analysis above. Relationships between changes

in these two variables and mean hippocampal PC were tested separately via Pearson correlation. Post-hoc tests were conducted to determine which nodes within the hippocampal module contributed to significant group difference. To test whether results were specific to negative symptoms, associations with change in positive symptoms were also tested.

Mediation analysis. A mediation analysis using the causal steps strategy (Baron & Kenny, 1986) was employed to test whether HC centrality, measured as mean hippocampal PC, mediated the relationship between the rates of change in verbal memory and negative symptoms. An alternative model was also explored wherein rate of change in verbal memory mediated the relationship between HC centrality and rate of change in negative symptoms.

Data Availability. Data is available from the authors upon reasonable request.

RESULTS

Sample. The final sample comprised 27 FEP patients (Female, 9) and 29 healthy controls (Female, 13) with longitudinal neuroimaging data (**Table 1**). For patients, 15 contributed two timepoints, 6 contributed three, and 6 contributed four timepoints. For controls, 9 contributed two, 7 contributed three, and 13 contributed four timepoints. Patients had significantly less years of education, lower performance IQ and lower scores on logical memory (defined as the average between immediate and delayed recall scaled scores). Patients and controls did not differ in age, sex, verbal IQ or rate of change in logical memory scores. For patients, baseline scans were acquired approximately 2.2 months (standard deviation [SD]=0.9 months) after entry to the PEPP clinic. Mean interscan intervals were as follows: 4.00 months (SD=0.76) between baseline and second scan, 6.04

(SD=0.62) between second and third scans, and 6.09 (SD=0.35) between third and fourth scans. See Supplementary Information for additional details.

Verbal memory and negative symptom relationships. Generally, patients had an improving course of negative symptoms (Mean=-12.7/year or -1.1/month, SD=17.0/year or 1.42/month) and verbal memory performance (Mean=2.7/year or 0.23/month, SD=5.3/year or 0.44/month) over the 4 to 16-month time window investigated. Rates of change in immediate and delayed recall were significantly and positively correlated with each other ($r=0.92$, $p<0.001$). Thus, verbal memory performance always refers to the average scaled score of immediate and delayed recall from the logical memory subtest of the WMS-IV. We found a significant relationship between rate of change in verbal memory and change in negative symptoms, whereby greater improvement in verbal memory performance was associated with improvement in negative symptom severity ($r=-0.59$, $p=0.018$).

Group differences in DAC. DAC matrices of hippocampal-intracortical regions were compared between patients and controls, where 280 pair-wise regions out of 3160 possible pairwise comparisons (FDR-corrected, $p<0.05$) had significantly different DAC in patients compared to controls (**Figure 2**). Patients showed both increased and decreased coupling between regions compared to controls across widespread brain regions, both within and across hemispheres. There were also notable patterns of altered coupling within the hippocampal circuit, seen by the dense pattern of differences in the bottom right of the matrices in **Figure 2**. See Supplementary Figure 2 for group differences in intracortical qT1 and Supplementary Table 2 for group differences in hippocampal/white matter qT1.

Group differences in PC of the hippocampal module. Patients exhibited significantly lower PC compared to controls ($F_{1,52}$=7.98, p=0.007) (**Figure 3A**). Post-hoc tests revealed that 7 of the 18 regions (p<0.05) in this module contributed to the lower PC in patients: CA1 and alveus bilaterally; left subiculum and fornix; right fimbria (**Figure 3B**). A similar trend was observed when calculating hippocampal PC from the first two timepoints for each subject only ($F_{1,52}$=3.52, p=0.066 (Supplementary Figure 3).

Group differences in PC of cortical modules. There were no significant group differences in mean PC for other cortical modules (Supplementary Figure 4).

Brain-behaviour relationships in FEP. The interaction of rates of changes in negative symptoms and verbal memory were evaluated against the mean PC of the hippocampal module. The overall model, including age and sex as covariates, was not significant ($F_{1,19}$=1.56, p=0.22); the interaction term was also not significant (t=0.49, p=0.63). We did not covary for antipsychotic medication[1] as we found no association between the hippocampal PC and medication (r=-0.0087, p=0.97).

Next, rate of change in negative symptoms and verbal memory were assessed separately against hippocampal PC. For rate of change in negative symptoms, a significant negative association emerged (r=-0.44, p=0.029), such that improvement in negative symptoms was associated with a higher mean hippocampal PC. For verbal memory, a significant positive association emerged (r=0.40, p=0.045), such that a more positive slope of verbal learning was

[1] Calculated as average daily dose across the study time period in chlorpromazine equivalents, multiplied by medication adherence

associated with a higher mean hippocampal PC. No significant association was found between the hippocampal PC and change in positive symptoms (r=-0.022, p=0.92).

Post-hoc tests were applied to assess the relationship between change in negative symptoms and change in verbal memory against individual hippocampal regions, restricting analyses to the regions that were uncovered above with significant group differences (**Figure 3C**). With respect to change in negative symptoms, significant negative associations were found with the PC of the right fimbria and left mammillary body (p's<0.05). For change in verbal memory, significant positive associations were found with the PC of the left alveus and right fimbria (p's<0.05).

Brain-behaviour relationships with cortical modules. No significant relationships between negative symptoms nor verbal memory were found with the PC of other cortical modules (Supplementary Table 3).

Mediation analysis. Our first mediation model, placing HC centrality as a mediator between changes in verbal memory and negative symptoms, was not significant. In contrast, our second model suggested that rate of change of verbal memory mediates between HC centrality and rate of change in negative symptoms (**Figure 4**).

DISCUSSION

This study provides novel evidence for reduced longitudinal coupling between hippocampal microstructure and cortical regions after psychosis onset. Our results demonstrate the important role of the hippocampal circuit (subfields and surrounding white matter) underlying the trajectory

of negative symptoms after FEP; a relationship which is mediated by changes in verbal memory. Our results suggest that changes in putative myelin content within the hippocampus are coupled to intracortical microstructure in healthy controls (as observed by higher PC); on the other hand, the lower PC observed in FEP, interpreted as decreased hippocampal centrality, suggests increased divergence of the hippocampal circuit from other cortical regions, particularly in patients with a worsening course of negative symptoms and verbal memory. Importantly, we did not find reduced centrality or relationships with negative symptoms and verbal memory deficits when examining the PC of other cortical networks.

The notion of the hippocampus being a central component of psychosis pathophysiology has been proposed previously (Lieberman et al., 2018; Tamminga et al., 2010). This study adds a novel perspective, suggesting that reduced hippocampal centrality may also give rise to negative symptoms. Further, we uncovered an explanatory framework for this relationship, wherein verbal memory mediates the association between altered DAC in hippocampal-intracortical microstructure and negative symptoms. Although our approach did not allow us to define the precise neocortical regions that drive this relationship of altered centrality, it may be relevant to consider links between the hippocampal cortex and fronto-temporal regions for several reasons: i) there is evidence for progressive brain changes in fronto-temporal cortices in patients with psychosis, including the transition to psychosis (Cannon et al., 2015) and after a FEP, that is unlikely to be confounded by medication (N. C. Andreasen et al., 2011; DeLisi, 2008; Olabi et al., 2011; Pantelis, 2005); ii) there is empirical evidence for direct connectivity between the hippocampus and medial temporal lobe, as well as between the hippocampus and prefrontal cortex(Simons & Spiers, 2003); iii) altered intracortical myelin has been noted in patients with enduring schizophrenia and other psychotic disorders within the prefrontal cortex (Lake et al.,

2017; Tishler et al., 2018; Wei et al., 2017);and iv) HC-medial temporal lobe and hippocampus-PFC subserve memory, emotional expression and motivational behaviours (Pier, Marin, Wilsnack, & Goodman, 2016; Schulze, Schmahl, & Niedtfeld, 2016; Squire, Stark, & Clark, 2004), which underlie verbal memory deficits and negative symptoms. Indeed, altered frontal connectivity has previously been linked to negative symptom severity (Luck et al., 2011).

Initially, we hypothesized that the hippocampus plays an important role with regards to changes in both verbal memory and negative symptoms, given the known links between the hippocampus and prefrontal cortical regions that subserve both of these constructs and prognostic indicators. However, our results suggest that despite being associated with each other, verbal memory deficits may not initially stem from abnormalities within the hippocampus and linked circuitry. It is known that verbal memory deficits exist before the onset of psychotic symptoms, and are also present in non-affected relatives of patients (Sheffield, Karcher, & Barch, 2018) and individuals with sub-threshold symptoms (Bonnín et al., 2012). It has also been proposed that the biological risk for verbal memory deficits can predict conversion to psychosis in the clinical high-risk state (Cannon et al., 2016; Seidman et al., 2016). Further work is required to understand the biological mechanism underlying verbal memory deficits seen in psychosis, but hippocampal dysfunction may play a key role across different stages of the disorder. This work also contributes to our knowledge of the interplay between verbal memory and negative symptoms. It has been shown that verbal memory deficits are stable across time in patients with persistent negative symptoms (Hovington et al., 2013), and that baseline verbal memory deficits are associated with higher levels of negative symptom severity cross-sectionally (Cirillo & Seidman, 2003; Makowski, Lewis, Lepage, Malla, Joober, Evans, et al., 2019). However, there is a need to study these complex clinical factors in a more dynamic fashion (Makowski, Lewis, Lepage, Malla, Joober, Evans, et

al., 2019). Here we found a robust association between worsening or little improvement in verbal memory and increased or little improvement in negative symptom severity in the 4 to 16 month period after a FEP. This finding highlights the importance of studying longitudinal relationships not only at the level of the brain structural "connectome", but also at the level of behaviour; and particularly for neurocognitive deficits which may not always be as stable as previously thought (Carrión et al., 2015; Green & Harvey, 2014).

Finally, we also tested the contribution of individual hippocampal subregions to the reduced centrality of the hippocampal circuit. We found that regions closer to the output of the hippocampal formation (subiculum, CA1, alveus, fimbria, fornix) were driving this effect and influencing the relationship between HC centrality and either negative symptoms or verbal memory. Indeed, other studies have also pinpointed structural alterations within the CA1 subfield and the fornix in FEP (Baglivo et al., 2017; Baumann et al., 2016). These regions are ideally positioned as putative hubs of the hippocampal circuit, and may be critical for transferring neural signals integrated within the hippocampus to broader cortical regions. Over adolescence and early adulthood, there is increased communication between such hub regions and "non-hubs" (Cao et al., 2014; Gu et al., 2015), as well as more extensive interactions between regions that are distal to each other (Fair et al., 2009). A relevant study showed that over 14-24 years of age, cortical hub regions (i.e. association areas including prefrontal and temporal regions) are characterized by a steep rate of intracortical myelination (Whitaker et al., 2016). Intriguingly, these regions are enriched for genes associated with schizophrenia risk. Our works suggests that previously reported alterations in intracortical myelination of higher-order association areas in psychotic disorders (Lake et al., 2017; Tishler et al., 2018; Wei et al., 2017) may be influenced by altered covariation with hippocampal microstructure, driven by hippocampal output regions or "hubs", and this may underlie the noted

observations with negative symptoms and verbal memory.

Findings of the hippocampus being central to negative symptoms and verbal memory deficits offer a new therapeutic avenue, either through the use of pharmacological and/or cognitive interventions known to impact the hippocampus. A class of pharmacological agents that may be promising in this regard are those with partial agonism at serotonergic receptors (e.g. 5HT1A), which differs from the mechanism of action of "typical" antipsychotic medications on dopamine signaling blockade. This would include currently available antipsychotic medications such as lurasidone and aripiprazole, as well as non-antipsychotic agents such as buspirone, all of which have been reported to have a positive impact on cognitive function in schizophrenia (Harvey et al., 2013; Riedel et al., 2010; Sumiyoshi et al., 2007), and may even have potential to decrease negative symptoms (Ogasa, Kimura, Nakamura, & Guarino, 2013). Further, our group has shown that an increase in hippocampal volume can be observed over a one-year treatment period specifically in FEP patients taking aripiprazole (Bodnar et al., 2016). Behavioural interventions could also provide promising avenues. Of interest, there is extant literature on the effects of physical exercise on the hippocampus. Exercise has been shown to increase hippocampal volume in older adults (Erickson et al., 2011), compared to the hippocampal volume loss that is characteristic of ageing. The authors also showed that hippocampal volume increases were accompanied by increases in levels of brain-derived neurotrophic factor (BDNF, a marker for neurogenesis and neuronal growth) and improvements in memory functioning. This sort of hippocampal plasticity in response to exercise, co-occurring with short-term verbal memory improvements, has also been demonstrated in patients with schizophrenia (Pajonk et al., 2010). Provided this evidence, it would be intriguing to test whether a combination of physical exercise

and novel pharmacological interventions may help repair hippocampal-cortical connectivity and in turn, ameliorate negative symptoms.

The current findings also hold promise in advancing knowledge of treatment transdiagnostically, as verbal memory deficits and negative symptoms are found in many other neurological and psychiatric disorders (Brown & Pluck, 2000). Negative symptoms, particularly those which impact goal-directed behavior, can be observed in human immunodeficiency viruses (HIV), Alzheimer's disease, Parkinson's disease, melancholic depression, and multiple sclerosis, to name a few (Brown & Pluck, 2000). Verbal memory deficits are also present in obsessive compulsive disorder, post-traumatic stress disorder, and various neurodevelopmental disorders (Gunstad, Paul, Cohen, Tate, & Gordon, 2006; Kavanaugh et al., 2016; Kikul, Van Allen, & Exner, 2012; Nichols et al., 2004; Wild & Gur, 2008). The hippocampus has also been posited to be an important pathophysiological component for many of these disorders, for instance depression (Roddy et al., 2019; Sheline, Liston, & McEwen, 2019) and epilepsy (Saling, 2009). Indeed, more studies are beginning to address the biological overlap between various classes of disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Crossley et al., 2014; Lange et al., 2018; C. H. Xia et al., 2018), moving away from the limitations of classical diagnostic frameworks, and opening up a future where brain disorders are treated in a more mechanistic and dimensional manner.

Several limitations of this work are considered. We have largely interpreted qT1 as a marker of myelin (Deoni, 2010; Tardif et al., 2018) in deriving evidence for the existence of myelin and microstructural alterations in psychotic disorders. However, alterations in T1 can be due to other factors, such as inflammation, reduced water content or altered iron content (Deoni, 2010). It is also acknowledged that for patients and controls who only contributed two timepoints, our ability

to map longitudinal changes was limited compared to participants with more timepoints. At the behavioural level, changes in verbal memory scores might be confounded by practice effects, given that the same test was used for each timepoint. One study has shown that such practice effects with the Weschler Memory Scale become much weaker after longer periods between testing (i.e. up to ~3 months) (Holdnack, Drozdick, Iverson, & Chelune, 2013). Thus, given our timeline, practice effects are likely not playing a major role. Our approach of measuring changes in negative symptoms linearly may also have been limited in capturing the extent of symptom fluctuations. Further, most patients had improved negative symptomatology over the course of the study, a finding which is line with what has been previously found by our group (Lutgens et al., 2019). However, it is unclear whether this trajectory can be explained by improvements in other symptom domains, given that negative symptoms can often be confounded or inflated by depressive symptomatology (Kirschner, Aleman, & Kaiser, 2017). It is also acknowledged that our patient sample is quite heterogeneous in terms of diagnosis, where we have included both affective and non-affective psychosis. Negative symptoms can be challenging to study in affective psychosis populations; however, negative symptoms have been reliably observed in patients with affective psychosis (Grove et al., 2016; Guessoum, Le Strat, Dubertret, & Mallet, 2020; Sauvé, Brodeur, Shah, & Lepage, 2019; Strauss et al., 2018; Strauss, Vertinski, Vogel, Ringdahl, & Allen, 2016). We have also previously controlled for diagnosis in our brain imaging studies of negative symptoms, finding that results are not altered (Makowski, Bodnar, Malla, Joober, & Lepage, 2016; Makowski et al., 2017).

The results of the current investigation suggest that the hippocampus serves as a catalyst in the dysconnectivity characterizing psychosis. Importantly, the hippocampus is a structure with high potential for plasticity; thus, treatments that can effectively ameliorate hippocampal structure

and/or function may also have downstream impact on negative symptomatology. Trajectories in verbal memory may also be an important behavioural marker paralleling the changes occurring in hippocampal microstructure and negative symptoms.

ACKNOWLEDGMENTS

We would like to thank PEPP-Montreal and Lepage Lab research staff for their efforts in recruitment and clinical data collection. We are also grateful to all patients and families for participating in the study. We would also like to thank Gabriel Devenyi for help with image processing, and Gabriella Buck, Gabrielle Pochiet, and Rachel Rosengard for help with imaging quality control. The study was supported by grants from the Canadian Institutes of Health Research and the Otsuka/Lundbeck Alliance. It also benefited from computational resources provided by Compute Canada (www.computecanada.ca) and Scinet high performance computing (https://www.scinethpc.ca/niagara/). Salary awards include: Canadian Institutes for Health Research (CIHR; C.M., R.J., M.M.C., A.C.E., M.L.), Fonds de la Recherche en Santé du Québec (FRSQ; M.M.C., M.L., J.L.S., and R.J.), funding from the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains for Healthy Lives Initiative (C.M., A.C.E.), James McGill Professorship (M.L., A.C.E.) and Canada Research Chairs Programme (A.K.M.).

CONFLICTS OF INTEREST

M.L. reports grants from Otsuka Lundbeck Alliance, personal fees from Otsuka Canada, personal fees from Lundbeck Canada, grants and personal fees from Janssen, and personal fees from MedAvante-Prophase, outside the submitted work. R.J. reports receipt of grants, speaker's fees, or honoraria from AstraZeneca, BMS, Janssen, Lundbeck, Otsuka, Pfizer Canada, Shire, and Sunovion and royalties from Henry Stewart Talks. A.M. reports receipt of grants, fees, or honoraria

from Lundbeck and Otsuka. A.C.E. has received consulting fees from Biospective. L.P. reports personal fees from Otsuka, Janssen, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen, Sunovion and Otsuka outside the submitted work. The above-mentioned sponsors and funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

TABLE AND FIGURE CAPTIONS

Table 1. Demographics and clinical information.

For patients, 15 contributed two timepoints, 6 contributed three, and 6 contributed four timepoints. For controls, 9 contributed two timepoints, 7 contributed three, and 13 contributed four timepoints. General Information reflects measures at baseline. Duration of untreated psychosis and untreated illness refers to time in weeks between onset of psychotic symptoms and initiation of antipsychotic treatment, and onset of general mental health symptoms to initiation of antipsychotic treatment, respectively. Baseline scan past clinic entry reflects the time in months between entry to the PEPP-Montréal clinic and the patient's first scan. All variables present for both FEP patients and healthy controls were compared with an independent sample t-test, except for socioeconomic status (SES), where the non-parametric Mann Whitney U test was used. Adjusted degrees of freedom are presented for performance IQ, as the two groups did not have equal variance. Variables with significant group differences ($p<0.05$) are bolded with an asterisk. Square brackets reflect altered sample size for cases where individual patient data was missing. Note that for ΔSANS/SAPS (measuring negative and positive symptoms, respectively), a mean score of change in negative symptoms per year indicates that patients' symptoms generally improved. A mean positive score for ΔLogical Memory (indexing average change in immediate and delayed recall per year) indicates a general improvement.

[1] One patient initiated antipsychotic medication use 9 weeks prior to their FEP, thus their duration of untreated psychosis is technically "-9 weeks". This value influences the median quite markedly in this dataset. Removing this participant yields a mean duration of untreated psychosis of 21.0 weeks and a median of 4.5 weeks.

Figure 1. Image processing workflow.

Step 1: Sampling of qT1 map of MP2RAGE sequence for hippocampal-white matter circuit labels from MAGeT (left) and 4 intracortical surfaces. For the hippocampal-white matter regions of interest (ROIs), a mean qT1 value was obtained for each label. For intracortical surfaces, a qT1 value was sampled at each of 81 924 points/vertices along the surface, and then averaged across linked vertices.

Step 2: Definition of individual ROIs: 18 regions of hippocampal-white matter circuit, and 62 DKT regions for intracortical surfaces. Colours of text of 18 hippocampal-white matter regions correspond to colour of labels used in left-hand side image of Step 1.

Step 3: Calculation of Dynamic Anatomical Covariance (DAC), adapted from Khundrakpam et al (2017). In this schematic, *i* and *j* represent two different ROIs, and the numbers reflect timepoints. First, the slope or rate of change in qT1 between timepoint t_1 and t_2 is calculated. The same is done for region *j*. The cosine of the theta (θ) angle defining the difference between these two slopes is then calculated, representing the DAC for participants that contributed two timepoints only. For participants with more than two timepoints available (i.e. t_2 and t_3, and t_3 and t_4), this calculation is repeated and the product of the cosine of the θ angle of change between consecutive timepoints defines the DAC.

Step 4: Graph theory was applied to each individual's DAC matrix. Specifically, participation coefficient was calculated for each ROI, using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010). The equation for participation coefficient is depicted in step 4, where y_i is the participation coefficient for each node *i*, contained within a particular module *m*. *M* represents the entire set of modules, and k_i represents the degree or number of links for each node *i*. modules were defined *a priori*; one module included the 18 ROIS of the hippocampal-white matter circuit,

and the 7 other modules were based on functional networks (Rubinov & Sporns, 2010) defined by Yeo et al (Yeo et al., 2011). These 8 modules are shown in Supplementary Figure 1. For this manuscript, the participation coefficient of the hippocampal-white matter circuit was the primary module of interest and is represented by the green module in the bottom-right hand side of the figure.

Figure 2. Group differences in DAC matrices.

Left-hand side: FDR-corrected matrices of significant pair-wise group differences in DAC. Dark grey square surrounds regions of the hippocampal circuit.

Right-hand side*:* Visualization of significant results portrayed in matrices with BrainNet Viewer. Nodes are coloured by network (hippocampal circuit + 7 functional networks). Width of lines reflect strength of pair-wise group difference. Warm colours/yellow reflects pair-wise differences that show increased coupling in FEP compared to controls. Cool colours/blue reflects pair-wise differences that show decreased coupling in FEP compared to controls.

Figure 3. Results with hippocampal PC.

Panel A: Group differences in hippocampal PC. Boxplots overlaid on a scatterplot of the data. For the boxplots, the red line denotes the mean, light blue boxes are the 95% confidence intervals, dark blue boxes represent 1 standard deviation, and grey dots are individual data points.

Panel B: Results of post-hoc tests applied to the PC of individual regions making up the hippocampal circuit within the hippocampal-intracortical network. Seven of the 18 regions were found to have significantly lower PC in patients compared to controls ($p<0.05$). Significant regions are listed, where the colour of the text matches the colour of the region in the MRI-visualization of regions making up the hippocampal circuit. MRI labels on left hemisphere taken from a patient included in the study. Top right-hand corner includes an anterior view of the 3D brain surface with the position of sagittal slices indicated with vertical blue lines corresponding to the anatomical images.

Panel C: Brain-behaviour analyses. Correlations between participation coefficient of the hippocampal-white matter module (adjusted for age and sex) in the hippocampal-intracortical network and changes in negative symptoms and verbal memory. Analyses were restricted to hippocampal nodes that showed significant post-hoc group differences. Statistics in the table are Pearson r-correlations, and significant relationships with $p<0.05$ are bolded in the table.

Figure 4. ΔVerbal memory mediates the relationship between HC centrality and Δ negative symptoms.

Path b remains significant when controlling for HC centrality (r=-0.506, p=0.012; df 22). There are two statistics shown for Path c, denoting the relationship between HC centrality and Δ negative symptoms. Path c shows a significant relationship between HC centrality and change in negative symptoms, *not* accounting for impact of verbal memory. Path c' between HC centrality and change in negative symptoms is no longer significant when taking into account Δ verbal memory, indicating that Δ verbal memory statistically mediates the relationship between hippocampal centrality and Δ negative symptoms. Note that hippocampal centrality denotes the mean PC of the hippocampal module in relation to DAC with intracortical microstructure, adjusted for age and sex.

FIGURES & TABLES

Table 1. Demographic and Clinical Information

		FEP N=27		Controls N=29				
		N	**%**	**N**	**%**	**Statistic**	**df**	***p*-value**
General/ Baseline Measures	Female	9	33.30	13	44.8	χ^2= 0.77	2	0.38
	Right Handed	22	81.5	29	100			
	Diagnosis							
	Schizophrenia Spectrum	10	37.0					
	Affective Disorder	11	40.7					
	Psychosis Not Otherwise Specified	6	22.2					
		Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Statistic**	**df**	**p-value**
	Age at Baseline	23.4 (3.5)	19.1-31.6	25.1 (4.1)	18.7-33.1	t=1.6	54	0.1
	Education in Years	12.7 (2.6)	6-18	14.2 (1.90)	10-17	t=2.6	54	0.01
	Socioeconomic Status	2.9 (1.0) [25]	1-5	3.3 (1.1)	1-5	U=277.5		0.1
	Performance IQ	102.5 (14.1)	70-127	111.3 (7.8)	96-128	t=2.8	39.9	0.007
	Verbal IQ	101.4 (13.0)	71-119	105.6 (10.9)	79-132	t=1.3	54	0.2
	Logical Memory	6.8 (2.9)	1.5-13.0	10.4 (2.7)	2.0-14.5	t=4.8	54	<0.001
	SANS	12.2 (9.0) [26]	1-31					
	SAPS	18.3 (17.1) [26]	0-49					
	Duration Untreated Psychosis (weeks) [1]	20.5 (31.5) [25] Median: 6.6	-9- 98					
	Duration Untreated Illness (weeks)	401.8 (313.6) [25] Median: 399.6	0-1219					
	Baseline scan past clinic entry (months)	2.2 (0.9)	0.7-3.5					
		Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Statistic**	**df**	**p-value**
Longitudinal Measures	ΔLogical Memory/year	2.7 (5.3) [26]	-10.2-12.0	2.5 (4.0)	-5.8-16.0	t=-0.2	53	0.9
	ΔSANS/year	-12.7 (17.0) [25]	-54.9-24.1					
	ΔSAPS/year	-24.5 (38.4) [25]	-118.5-24.4					
	Avg CPZ equivalents (daily dose in mg)	192.6 (194.5)	0-734.5					

Figure 1

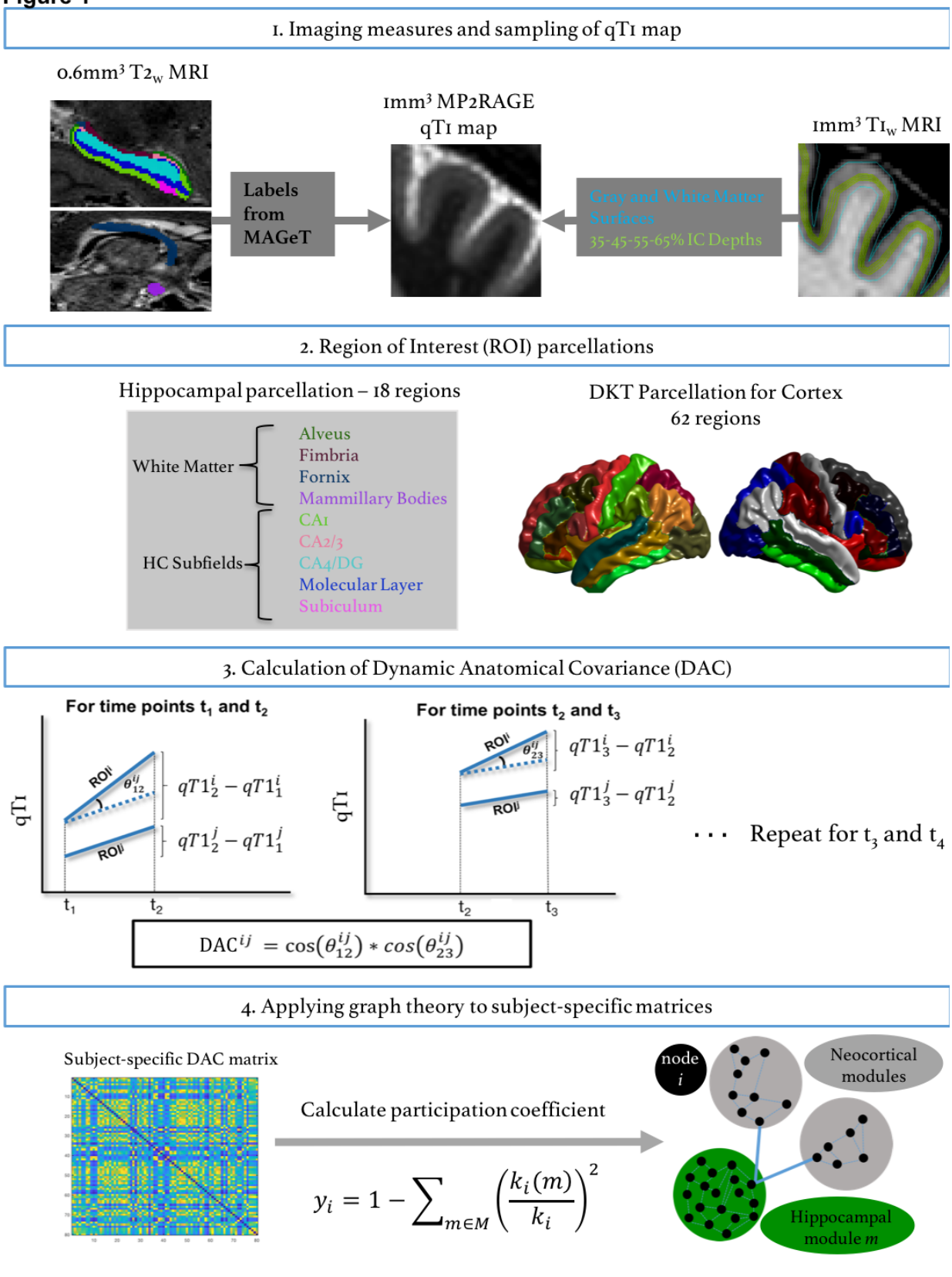

1. Imaging measures and sampling of qT1 map
0.6mm³ T2w MRI
1mm³ MP2RAGE qT1 map
1mm³ T1w MRI
Labels from MAGeT
Gray and White Matter Surfaces
35-45-55-65% IC Depths
2. Region of Interest (ROI) parcellations
Hippocampal parcellation – 18 regions
White Matter
Alveus
Fimbria
Fornix
Mammillary Bodies
HC Subfields
CA1
CA2/3
CA4/DG
Molecular Layer
Subiculum
DKT Parcellation for Cortex 62 regions
3. Calculation of Dynamic Anatomical Covariance (DAC)
For time points t1 and t2
For time points t2 and t3
qT1
ROIi
ROIj
$qT1_2^i - qT1_1^i$
$qT1_2^j - qT1_1^j$
$qT1_3^i - qT1_2^i$
$qT1_3^j - qT1_2^j$
· · · Repeat for t3 and t4
$DAC^{ij} = \cos(\theta_{12}^{ij}) * cos(\theta_{23}^{ij})$
4. Applying graph theory to subject-specific matrices
Subject-specific DAC matrix
Calculate participation coefficient
$y_i = 1 - \sum_{m \in M} \left(\frac{k_i(m)}{k_i}\right)^2$
node i
Neocortical modules
Hippocampal module m

Figure 2

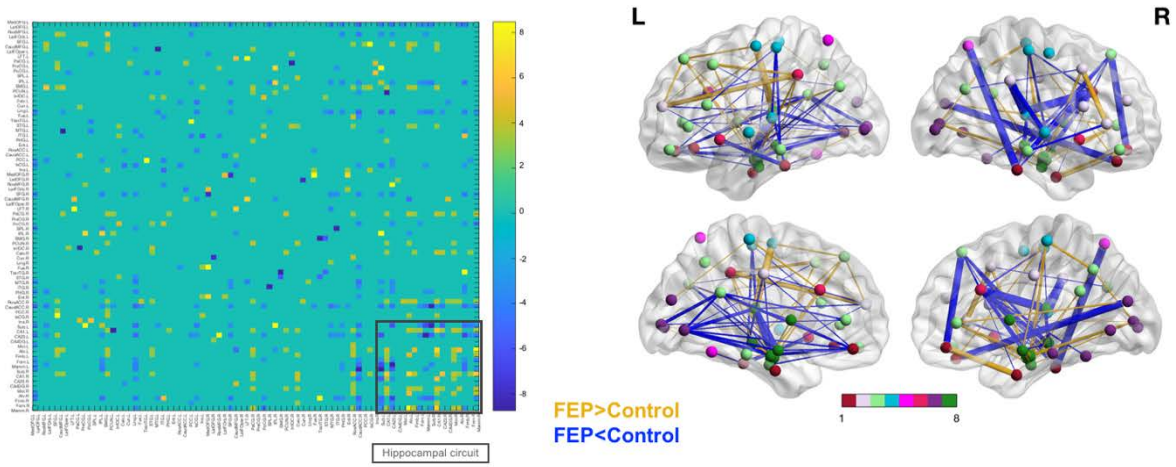
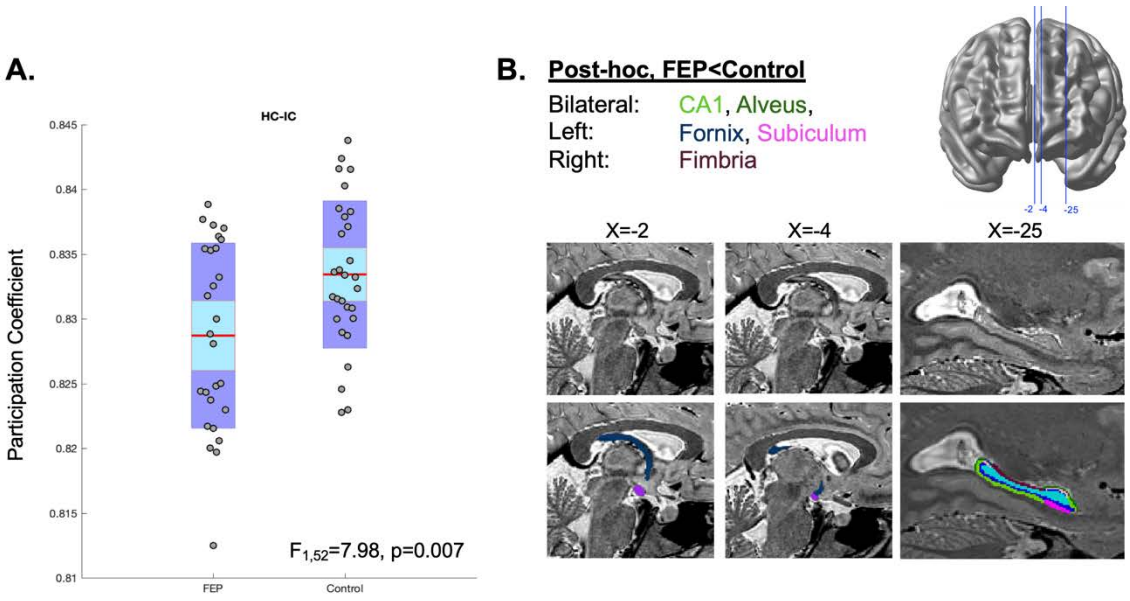


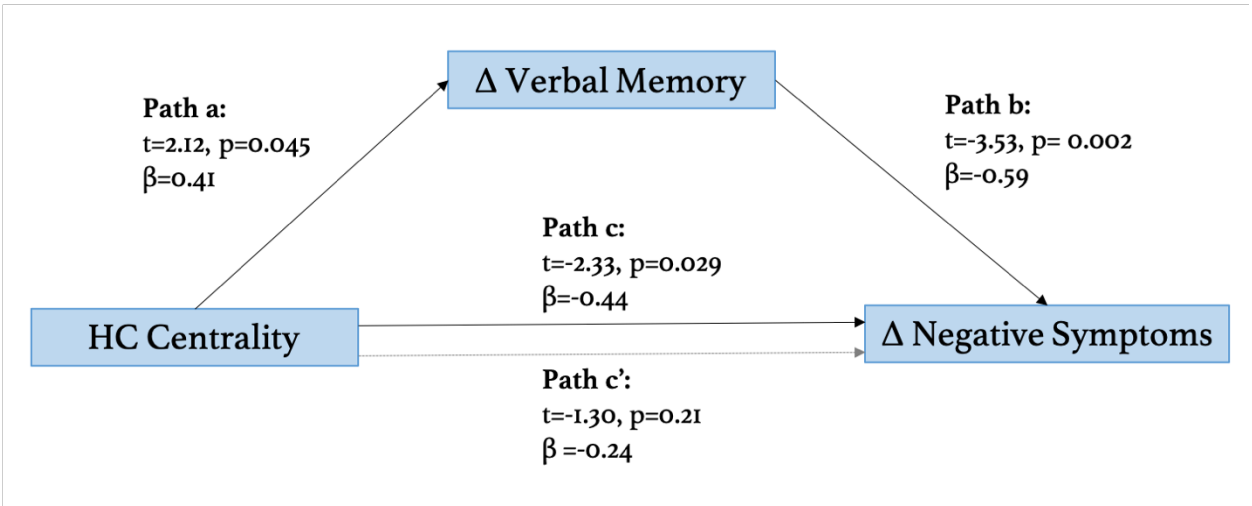
Figure 3



C.

	Δ Negative Symptoms		Δ Verbal Memory	
HC Node	**Left**	**Right**	**Left**	**Right**
CA1	-0.1	-0.21	0.26	0.29
CA2/3	-0.24		0.2	
CA4/DG				
Subiculum	-0.21		0.29	
Molecular layer				
Alveus	-0.38	-0.27	**0.46**	0.34
Fimbria		**-0.44**		0.34
Fornix	0.073	-0.34	-0.17	**0.41**
Mammillary Body	**-0.53**		0.37	

Figure 4


Δ Verbal Memory
Path a:
t=2.12, p=0.045
β=0.41
Path b:
t=-3.53, p= 0.002
β=-0.59
Path c:
t=-2.33, p=0.029
β=-0.44
HC Centrality
Δ Negative Symptoms
Path c':
t=-1.30, p=0.21
β =-0.24

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