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Hippocampal Volume and Functional Connectivity with the Default Mode Network

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Hippocampal Volume and Functional Connectivity with the Default Mode Network

By

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B.A., Syracuse University, 2015

Advisor: Elaine F. Walker, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
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Abstract

Hippocampal Volume and Functional Connectivity with the Default Mode Network
By Katrina Aberizk

Hippocampal volume (HV) appears more sensitive to environmental exposures than other brain regions. Reductions in HV have been associated with psychotic illness, as well as other stressful experiences in both healthy and clinical populations. Associations between stress-related changes in brain structure and functional connectivity (FC) have been demonstrated in animal research, yet such cross-modal brain relationships remain poorly characterized in humans. To date, there has been limited investigation of the relationship between HV and hippocampal FC. The present study examined associations between bilateral HV and mean hippocampal FC with the default mode network (DMN) during rest in healthy controls (HC) and individuals at clinical high-risk for psychosis (CHR-P). The sample included 246 CHR-P (218 non-converters and 28 converters) and 143 HC from the second phase of the North American Prodrome Longitudinal Study. Matrix regression revealed significant negative associations between HV and hippocampal FC with the inferior parietal lobe and thalamus after correcting for multiple comparisons. There was a significant interaction between group and right hippocampal FC with the left superior temporal pole in associations including bilateral HV. In HC, FC between the right hippocampus and left superior temporal pole was negatively associated with bilateral HV. There was a positive association between these variables in CHR-P. This research contributes insights regarding hippocampal cross-modal brain relationships, and findings may have implications for the role of DMN subsystems. Potential underlying mechanisms and implications for future research are discussed.

Hippocampal Volume and Functional Connectivity with the Default Mode Network

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Table of Contents

Introduction

Relative to other brain regions, the volume of the hippocampus (HV) appears to be less determined by genetic factors and more sensitive to environmental influences. Studies of healthy monozygotic (MZ) twins (Sullivan et al., 2001) and investigations of genetic influence (Peper et al., 2007; Kremen et al., 2010) have revealed lower heritability estimates for HV than the volumes of other brain areas, indicating that environmental factors play a substantial role in determining HV. Consistent with that notion, the hippocampus plays a substantial role in the neurobiological systems governing the stress response, and stress has been implicated as a significant contributor to reductions in HV in healthy samples (Tessner et al., 2007; Samplin et al., 2013; Hodel et al., 2015; Davis et al., 2017; Merz et al., 2019). Despite evidence that there is considerable variability in HV both between groups (Woon et al., 2010) and within-subjects over time (Bauduin et al., 2018; Ott et al., 2019), little is known about hippocampal cross-modal brain relationships; in other words, how changes in the functional connectivity (FC) of the hippocampus may be associated with changes in HV (i.e., functional to structural relations). Importantly, the hippocampus serves as a functional hub (i.e., involving particularly well-connected nodes or regions) in multiple brain networks subserving several sensory, associative, and cognitive processes (Edmiston et al., 2020). The present study is concerned with the relation of HV with resting-state FC (i.e., functional brain imaging in the absence of cognitive demands) in healthy individuals and those at clinical high-risk for psychosis (CHR-P).

Reductions in HV have been associated with stressful exposures involving the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a neuroendocrine system regulated in part by negative feedback via glucocorticoid receptors in the hippocampus (Walker et al., 2010; Holtzman et al., 2013). Under conditions of mild or acute stress, normative activation of

the HPA axis promotes allostatic processes in the brain; these include increases in synaptic plasticity, memory enhancement, and improved decision-making, putatively reflecting the adaptive importance of recalling threatening stimuli and reacting to subsequent stressors (McEwen & Gianaros, 2011; McEwen & Akil, 2020). However, if stressors become chronic or repeated, adverse effects on brain structure and function may be observed (Vinson, 2009; McEwen & Morrison, 2013; Eiland & Romeo, 2013; Chen & Baram, 2016; Pruessner et al., 2016).

Indeed, the hippocampus is rich in glucocorticoid receptors (e.g., cortisol in humans) and maintains a prominent role in glucocorticoid negative feedback throughout development, providing an extended period of hippocampal vulnerability to environmental insults (Carrion et al., 2007; Chen & Baram, 2016). Animal research has demonstrated dendritic atrophy in hippocampal subfields following chronic stress (Brunson et al., 2005; Ivy et al., 2010), and studies of humans have shown that chronic stress is associated with structural abnormalities in the hippocampus (Herman et al., 2005). Hippocampal integrity is also relevant to cognitive function; research with rodent and human subjects has revealed inverse associations between hippocampal subfield volumes and cognitive task performance, especially learning and memory (Leutgeb et al., 2007; Tamminga et al., 2010; Vargas et al., 2018). Relatedly, animal and human research consistently associates chronic stress with impaired memory performance (Kim & Diamond, 2002; McEwen & Gianaros, 2011; Schwabe et al., 2011).

Consistent with the notion that prolonged exposure to endogenous glucocorticoids may have implications for the integrity of the hippocampal formation in humans, numerous studies of both healthy and clinical samples have demonstrated an inverse relation between stressful exposures and HV including studies of healthy youth (Davis et al., 2017; Merz et al., 2019) and

adults (Tessner et al., 2007; Samplin et al., 2013; Hodel et al., 2015), and individuals with major depressive disorder (Moica et al., 2016, Travis et al., 2016; Geerlings & Gerritsen, 2017), post-traumatic stress disorder (Woon et al., 2010), chronic schizophrenia (SCZ) (van Erp et al., 2015; Okada et al., 2016), and first-episode psychosis (FEP) (Steen et al., 2006; Mondelli et al., 2010), suggesting that HV reductions reflect nonspecific vulnerability to serious mental illness (Chen et al., 2020). A recent systematic review and meta-analysis, including participants from the present sample (Cannon et al., 2015), concluded that there are no significant differences in bilateral HV between HC and CHR-P (Walter et al., 2016); however, a recent study observed reduced bilateral HV in CHR-P (Vargas et al., 2019), and other work segmenting the hippocampus by subfield in CHR-P has found significantly reduced bilateral CA1 (Ho et al., 2017) and bilateral CA1, CA2/3, and dendate gyrus volume (Vargas et al., 2018) compared to HC. It is noted that the majority of studies included in the 2016 review (Walter et al., 2016) used manual tracing to extract the hippocampus from structural images, while contemporary approaches have used automated methods. It should also be noted that samples of CHR-P youth are heterogeneous, and estimates suggest only 20-30% of CHR-P will eventually manifest psychotic symptoms (Brucato et al., 2017; Velthorst et al., 2019). Thus, power for detecting differences between HC and CHR-P samples is reduced.

Overall, HV reductions have been observed across the psychosis spectrum, and there is evidence that these changes are partially genetic in origin. While polygenic risk scores (PRS) for SCZ have been associated with reductions in right HV (Liu et al., 2020), and reductions in left HV have been observed in non-psychotic, first-degree relatives of SCZ (Seidman et al., 2014), studies of MZ twins discordant for SCZ have found substantial bilateral reductions in HV in the affected compared to non-affected co-twin (Narr et al., 2002; Van Haren et al., 2004; van Erp et

al., 2004), again suggesting environmental exposures (e.g., stressful life experiences associated with chronic psychiatric illness) contribute to a reduction in HV beyond that conferred by genetic vulnerabilities. In healthy subjects, research has found that stressful life events can also cause alterations in the expression of genes related to the HPA axis structure and function (Heim et al., 2008, 2010; Klengel et al., 2013). Recent longitudinal work assessing how chronic unpredictable stress impacts the structure and function of the rodent brain suggests important associations between structural and functional alterations; in particular, stress-induced volumetric reductions in key regions such as the cortex, thalamus, striatum, and hippocampus, were associated with increasing FC within a network composed by these regions (Magalhães et al., 2018).

Despite the evidence that reduced HV is associated with both adverse environmental factors and psychosis, little is known about the relation of HV with brain connectivity, or hippocampal cross-modal brain relationships (i.e., brain structure to function) in healthy individuals, SCZ, or at-risk populations. During a working memory task, Harms and colleagues (2013) found reduced HV in SCZ patients to be significantly associated with reduced activity in regions subserving working memory, consistent with prior work (Leutgeb et al., 2007; Tamminga et al., 2010; Vargas et al., 2018). In a sample of 27 biological relatives of SCZ patients, Seidman and colleagues (2014) found that left hippocampal and posterior parahippocampal volumes were significantly inversely associated with brain activity in regions subserving internal narrative during task performance. Specifically, reduced left HV was associated with reduced suppression of internally-directed thought and putatively interfered with cognitive function. To date, only one reported study has examined the relation of HV with task-free resting state functional magnetic resonance imaging (rsfMRI) in SCZ. Liu and colleagues

(2020) calculated PRS for SCZ and tested the association of the PRS with both HV and hippocampal FC in 509 SCZ patients and 502 HC. They found that PRS for SCZ was inversely associated with right HV, again indicating that genetic risk for SCZ contributes to reductions in HV. Next, they examined rsfMRI, which relies on a blood oxygenation-level dependent (BOLD) signal to measure spontaneous covariance in neural activity at specified regions in the brain during periods of rest (Mevel et al., 2011; Chen et al., 2018), selecting the right hippocampus as a seed region of interest. They found that the PRS for SCZ was associated with reduced connectivity strength between the hippocampus and medial prefrontal cortex (mPFC), suggesting that greater genetic risk for SCZ is linked with both reduced HV and hippocampal connectivity with the mPFC.

The mPFC is a major hub in the default mode network (DMN), a brain network involved in self-reflection, internal narrative, cognitive and social processing (Pomarol-Clotet et al., 2010, Menon, 2011; Seidman et al., 2014; Padula et al., 2017), and also which has attracted considerable interest in research on SCZ (Swanson et al., 2011; Fox et al., 2017). The DMN, sometimes referred to as a resting-state network, consists of a set of brain areas (i.e., nodes) more engaged during rest than cognitive tasks (Hutchinson et al., 1999). DMN activity, characterized as synchronized, low-frequency oscillations of brain activity in distributed nodes, is measured by assessing the temporal characteristics of metabolic demand (Mevel et al., 2011). While the DMN exhibits strong internal consistency in healthy populations (Mevel et al., 2011), there are divergent findings on DMN connectivity in psychosis. Some studies of rsfMRI (Zhou et al., 2007) and task-based fMRI (Whitfield-Gabrieli et al., 2009) have reported increases in DMN activity in SCZ compared to HC subjects, while others using both acquisition methods report more complex diagnostic group differences. For example, one study revealed that SCZ patients

showed increased FC within more posterior cortical and subcortical regions, whereas HC showed greater FC within anterior cortical regions (Mannell et al., 2010). Other studies of SCZ have reported decreases in DMN activity during rsfMRI (Bluhm et al., 2007; Jang et al., 2011), and still others report no significant difference between SCZ and HC during rsfMRI (Fox et al., 2017). Some have suggested that increased DMN activity during task-based fMRI reflects an impaired capacity to suppress DMN activity, thus interfering with cognitive task performance (Seidman et al., 2014), yet it remains unclear how DMN activity may be associated with structural changes within the network in the absence of cognitive demands.

rsfMRI studies of the psychosis spectrum also report mixed findings; investigations of within-DMN activity have found weaker positive FC between the mPFC and posterior cingulate cortex (PCC) in FEP (Alonso-Solis et al., 2012), weakened inferior temporal connectivity (Shim et al., 2010) and increased global DMN activity (Clark et al., 2018) in individuals at CHR-P, and decreased DMN connectivity in adolescents reporting psychotic-like experiences (Amico et al., 2017; Karcher et al., 2019). In one of the largest longitudinal studies of individuals at CHR-P, the North American Prodrome Longitudinal Study (NAPLS), individuals who subsequently developed psychosis demonstrated a progressive decrease in within-DMN efficiency during rest which was shown to contribute to an overall decrease in brain network efficiency, as indexed by an increase in path length between nodes and a decrease in the consistency of FC organization over time (Cao et al., 2019). Given the heterogeneity among SCZ patients in symptom profiles, genetics, neurobiological measures, response to treatment, and illness course, it is now assumed that there is etiological heterogeneity with multiple neural pathways leading to clinical expression of SCZ (Gratton & Mittal, 2020). Further, samples differ in composition by nature and dose of psychotropic medications which could influence both task-based and rsfMRI (Duan

et al., 2020). It is, therefore, not surprising that research on connectivity yields inconsistent findings that may reflect differences among samples in medication status or their representation of various etiologic subtypes.

Reductions in HV are, however, one of the most well-established findings from neuroimaging research on SCZ and other psychoses. Yet, little is known about the relation of HV with rsfMRI or DMN activity in either healthy or clinical samples. Although there is very limited evidence for hypothesizing causal directionality, animal work suggests that functional changes likely predate structural alterations (Magalhães et al., 2018), and it is possible that alterations in hippocampal FC may be present before global HV changes are observed. More broadly, given evidence that HV is sensitive to environmental exposures including air pollution (Hedges et al., 2019), socioeconomic status (Assari, 2020), and child abuse (Young et al., 2019), using the hippocampus as a seed region of interest (ROI) in investigations of cross-modal brain relationships may prove fruitful. Informed by similar rsfMRI investigations of HC (De Marco et al., 2019) and individuals with clinical symptoms of psychosis (Liu et al., 2020; Nelson et al., 2020), the present study aimed to examine associations between HV and hippocampal FC with all major nodes of the DMN [i.e., bilateral medial superior frontal (mSFC) and orbitofrontal regions (mOFC), anterior (ACC) and posterior cingulate (PCC), precuneus, parahippocampal and angular gyri, inferior parietal lobule (IPL), thalamus, and middle and superior temporal regions] as identified in prior work (Raichle et al., 2001; Zhao et al., 2007; Mannell et al., 2010; Mevel et al., 2011). Drawing on prior work (De Marco et al., 2019; Liu et al., 2020; Nelson et al., 2020), it was predicted that reduced HV would be associated with reduced DMN activity during rsfMRI, possibly reflecting a siphoning of metabolic resources from the DMN to other

regions connected with the hippocampus. There are no reports on hippocampal cross-modal brain relations in diagnosed psychosis patients or CHR-P.

Methods and Materials

Sample

The present sample included adolescents and young adults between the ages of 12 and 30 years from the second phase of the multi-site NAPLS study (NAPLS 2). The participants included in this study were those who had completed an MRI scan with an acquired T1-weighted structural image and rsfMRI data that passed quality assurance metrics (N = 389). This sample included 143 HC, 218 non-converters (CHR-NC; those who demonstrated attenuated psychotic symptoms at baseline but did not convert to psychosis by the completion of the two-year follow-up) and 28 converters (CHR-C; those who had clinical symptoms of psychosis by completion of the study). Briefly, all CHR-NC participants in the present study met criteria for attenuated psychotic symptom syndrome (APSS) on the Structured Interview for Psychosis Risk Syndromes (SIPS). All CHR-C participants in the present study met criteria for a score of "6" (i.e., severe and psychotic) on at least one positive symptom subscale of the SIPS at the two-year follow-up. The aims, recruitment methods, and inclusion criteria have been described elsewhere (Addington et al., 2012; Addington et al., 2017), and demographic characteristics of the present sample are presented in Table 1. All participants provided consent (or parental assent where appropriate) in accordance with relevant guidelines and regulations at the eight participating sites of the NAPLS 2 consortia.

Imaging Paradigm and Data Acquisition

Participants underwent a 5-minute eyes-open resting-state scan (rsfMRI). Details on data acquisition have been described in detail in previous reports (Cao et al., 2019). Briefly,

preprocessing of rsfMRI data was conducted through a combination of FSL tools (skull stripping, high-pass filtering, volume trimming, smoothing, registration, generation of motion covariates with *mcflirt*) and the CONN toolbox 19.c (denoising, detrending, despiking, low-pass filtering). Structural HV data were corrected for site and intracranial volume.

Data Processing

The entire processing pipeline followed that of previously published work (Cao et al., 2016; Cao et al., 2017). In brief, mean time series for each of the 116 nodes defined by the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) were extracted from the preprocessed data and further corrected for movement and scanner noises. Pairwise Pearson correlation coefficients were calculated between the processed time series of each node, resulting in a 116 x 116 two-dimensional (2D) correlation matrix for each subject.

Statistical Analysis

389 (i.e., N = 389) 116 x 116 2D correlation matrices were loaded into Matlab version 2019b to create an aggregate three-dimensional 116 x 116 x 389 matrix. The rows corresponding to bilateral hippocampal mean FC with all other nodes of the matrix were pulled, respectively, creating two 1 x 116 x 389 matrices. The singular dimension was removed from each matrix using *squeeze*, and the resulting 116 x 389 matrices were flipped using *transpose* so that each row corresponded to a single subject and each column corresponded to FC between right or left hippocampus, respectively, and all other regions of the AAL atlas; i.e., one 389 x 116 2D matrix for right hippocampal FC and one 389 x 116 2D matrix for left hippocampal FC. The column corresponding to seed (i.e., right or left hippocampus, respectively) FC with itself (i.e., a column of 1s) was removed from both matrices, creating two 389 x 115 2D matrices. Next, the nodes classified in the DMN were selected, as described above (n = 28); thus, two 389

x 28 2D matrices were maintained. A column of ones was then created at the first column of both matrices to be used as an intercept in matrix regression, i.e., two 389 x 29 matrices.

These matrices, corresponding to bilateral hippocampal FC with 28 nodes of the DMN, were loaded into R version 4.0.4 using the *R.matlab* package. Pearson's *r*s were transformed in both matrices to Fisher's *z* statistic using the *fisherz* function of the *psych* package. Vectors matching individual subject right and left HV, respectively, along with diagnostic group (coded as an ordinal variable where 1 = HC, 2 = CHR-NC, 3 = CHR-C) were also loaded into R using the *readxl* package. Using separate loops for matrix regression, bilateral hippocampal FC with each DMN node was regressed onto ipsilateral and contralateral HV (i.e., four models; left ipsilateral = left HV and left FC, left contralateral = left HV and right FC, right contralateral = right HV and left HC, right ipsilateral = right HV and right FC). In models examining potential moderation effects of diagnostic group, main effects for group and an interaction term between group and hippocampal FC (group*FC) were added. Unstandardized coefficients were bootstrapped with 10,000 samples using the *residual* method of the *Boot* function, which relies on the *car* and *boot* packages in R, and which resamples residuals rather than cases to treat predictors as fixed (Fox & Weisberg, 2012). This method was chosen as cases are fixed with respect to the parent connectivity matrices from which they were derived. Bias-corrected 95% confidence intervals were constructed using the *bca* method of the *confint* function of the *car* package. Significance levels were adjusted for multiple comparisons using the Benjamini-Hochberg method. Briefly, significance levels (n = 28 per loop) were ranked in ascending order alongside a vector of a = .05/1:28; thus, the lowest significance value from each matrix regression was subjected to a = .05, the next lowest value was subjected to a = .025, etc., with the highest significance value subjected to a = .05/28 = .0017.

Results

One-way analyses of variance (ANOVA) evaluating group differences in mean connectivity between the hippocampi and DMN nodes, as well as group differences in bilateral HV, are presented in Table 2. Briefly, ANOVA revealed significant group differences only in left hippocampal connectivity with the right (F = 2.95, p = .053) and left (F = 3.37, p = .035) precuneus. A post-hoc Tukey test revealed a significant difference in left hippocampal-left precuneus FC between HC and CHR-C, p = .032, with HC demonstrating greater mean connectivity strength between nodes; similarly, there was a significant difference in left hippocampal-right precuneus FC between HC and CHR-C, p = .048, with HC again demonstrating greater mean connectivity strength between the nodes. There were no significant differences in right (F = 1.26, p = .285) or left (F = .22, p = .799) HV between groups. Levene's test for homogeneity of variance was insignificant for left (F = 1.53, p = .217) and right (F = 1.65, p = .191) HV between groups.

Results of tests of relationships between HV and hippocampal FC are shown in Figure 1. After correcting for multiple comparisons in simple regression models (i.e., HV to FC relationships only), left hippocampal FC with the right inferior parietal lobe (IPL) was significantly inversely associated with left HV, β = - 277.99, p = .031, 95% CI = [- 529.76, - 23.68]. Right hippocampal FC with the left thalamus was significantly inversely associated with left HV, β = - 324.61, p = .014, 95% CI = [- 580.27, - 64.10]. Left hippocampal FC with the right IPL was significantly inversely associated with right HV, β = - 303.04, p = .014, 95% CI = [- 545.13, - 52.13]. Right hippocampal FC with the left IPL was significantly inversely associated with right HV, β = - 273.07, p = .029, 95% CI = [- 513.33, - 28.44] (Figure 1). Thus, in all cases, the relationship of HV with FC was inverse, such that smaller volume was associated

with greater FC. All nominally significant results are presented in Table 3.

Standardized residuals for all four models were examined using the *stdres* function of the *MASS* package in R; $n = 4$ standardized residuals had an absolute value greater than three in models including left HV, and, inclusively, $n = 2$ standardized residuals had an absolute value greater than three in models including right HV. Overall, $n = 4$ cases comprise approximately 1% of the total sample; in addition, 95% confidence intervals under normal theory were highly comparable with confidence intervals constructed with bootstrapping methods. An examination of Cook's distance of the relevant cases ($n = 4$) using base package tools in R did not reveal evidence of undue influence on respective models. The full sample was maintained in subsequent analyses.

Subsequent analyses tested whether the relation between hippocampal FC and HV was moderated by diagnostic group given observed differences in the direction and magnitude of the relation between groups (Figures 2–5). After accounting for main effects of FC and diagnostic group in each model, there was a significant interaction between group and right hippocampal FC with the left superior temporal pole in prediction of left HV, $\beta = 514.19$, $p = .009$, 95% CI = [131.26, 897.70]. After controlling for the same main effects, there was also a significant interaction between group and right hippocampal FC with the left superior temporal pole in prediction of right HV, $\beta = 385.16$, $p = .041$, 95% CI = [23.56, 753.90].

To unpack the significant interactions between group and right hippocampal-left superior temporal pole FC with bilateral HV, simple linear regression between the FC relation and right and left HV, respectively, was conducted in each group separately. Results of simple regression analyses were insignificant, but revealed differential associations between right hippocampal-left superior temporal pole FC with bilateral HV between the HC and CHR-P groups (i.e., negative

associations in HC, positive associations in CHR-NC and CHR-C). Results are presented in Table 4 and illustrated in Figures 6 and 7.

Discussion

Compared to other brain regions, the volume of the hippocampus appears to be more sensitive to environmental exposures (Sullivan et al., 2001; Peper et al., 2007; Kremen et al., 2010), and HV reductions are associated with a range of serious mental illnesses (Chen et al., 2020). In the case of SCZ, reductions in HV are one of the most well-established findings, with numerous studies of MZ twins finding significantly reduced bilateral HV in the affected compared to the non-affected co-twin (Narr et al., 2002; Van Haren et al., 2004; van Erp et al., 2004), further implicating environmental exposures in changes to HV. Recent work has observed reductions in HV in CHR-P (Ho et al., 2017; Vargas et al., 2018; Vargas et al., 2019), yet there are no studies directly associating hippocampal cross-modal (i.e., structure to function) brain relationships in CHR-P.

Prior work has also indirectly associated genetic risk for SCZ with both reductions in HV and reduced hippocampal connectivity with the mPFC (Liu et al., 2020), a major hub in the DMN (Pomarol-Clotet et al., 2010, Menon, 2011; Padula et al., 2017). While research findings on DMN connectivity in samples of psychotic or CHR-P individuals are inconsistent (e.g., Zhou et al, 2007; Jang et al., 2011; Swanson et al., 2011; Fox et al., 2017; Clark et al., 2018), no studies have directly examined whether any regional volumetric reductions within the DMN are associated with changes in FC in the absence of cognitive demands. Consistent with prior work indirectly associating HV with hippocampal connectivity during rest in HC (De Marco et al., 2019) and individuals with clinical symptoms of psychosis (Liu et al., 2020; Nelson et al., 2020), it was hypothesized that reductions in HV would be associated with reductions in hippocampal

connectivity, possibly reflecting a siphoning of metabolic resources away from the DMN to other brain regions connected with the hippocampus.

Contrary to this hypothesis, significant negative associations between HV and hippocampal connectivity with the IPL and thalamus were observed; smaller HV was associated with increased FC. Given the paucity of research on the relation of HV with hippocampal FC, especially experimental or longitudinal research, interpretation of these findings must be considered tentative. Nonetheless, the findings are consistent with several alternative interpretations that suggest directions for further investigations.

One possibility concerns the influence of shared developmental processes and environmental factors on both hippocampal-IPL/TPJ connectivity and HV. Hippocampal connectivity with the IPL may be particularly sensitive to changes in HV as hippocampal-IPL cross-modal relationships were nominally significant (Table 3) across all four models (i.e., left ipsilateral, left contralateral, right contralateral, right ipsilateral) and a majority of these associations survived correction for multiple comparisons. Consistent with the notion that the IPL may be sensitive to HV, prior work has found positive associations between bilateral HV and DMN connectivity in the right temporoparietal junction (TPJ) in healthy adults (De Marco et al., 2019). In the present study, significant inverse associations were observed between hippocampal-IPL connectivity and bilateral HV. Importantly, the IPL includes the overlapping TPJ, and the IPL/TPJ constitute a major hub in the DMN, are implicated in both bottom-up sensation and top-down cognitive processing, and mature late in human development, likely related to their recent phylogenetic history (Shenton et al., 2001; Igelström & Graziano, 2017). While phylogenetically older, the hippocampus also has a protracted developmental course (Carrion et al., 2007; Chen & Baram, 2016), and changes in HV have been shown to be

associated with stress (e.g., Steen et al., 2006; Mondelli et al., 2010; Hodel et al., 2015; Travis et al., 2016; Davis et al., 2017; Merz et al., 2019). The IPL appears to be sensitive to stressful exposures as well; research has found associations between allostatic load (i.e., a quantified index of multiple stress indicators) and reduced IPL thickness in both control subjects and patients with SCZ (Chiappelli et al., 2017). While rather speculative, it is possible that deviations in hippocampal-IPL/TPJ connectivity associated with HV are due in part to a shared protracted development rendering them particularly vulnerable to environmental influence.

It is also possible that the relations between HV and hippocampal FC detected in the present study reflect compensatory processes. Consistent with the notion that HV and compensatory changes in hippocampal FC appear to be closely related, a significant relationship between the right hippocampus and left thalamus was observed in prediction of left HV in the present study, such that increased connectivity between the hippocampus and thalamus was associated with reduced HV. This inverse relation may be related to the essential role of the thalamus for resource allocation and information transfer in the brain (Schiff, 2008). A recent study investigating associations between stress reactivity and brain network organization found increased network centrality in the thalamus to be significantly associated with higher subjective stress ratings during a laboratory stress task, and there were positive trends between thalamic network centrality, heart rate and salivary cortisol (Reinelt et al., 2019). It has been suggested that increased network centrality in the thalamus reflects increased alertness and information processing (Zhu et al., 2018), so if reductions in HV are indicative of persistent stress, at least to some degree, it is conceptually appealing to anticipate increases in the connectivity of the thalamus to be associated with decreases in HV, perhaps reflecting the adaptive importance of remaining vigilant in anticipation of subsequent stressors. Relatedly, successful treatment for

PTSD, which is also associated with reduced HV (Woon et al., 2010), appears to alter hippocampal FC. Zhu and colleagues (2018) found that PTSD patients who were successfully treated with exposure-based therapy showed increased amygdala and hippocampus connectivity with prefrontal cortical regions. The authors concluded that these changes might reflect compensatory changes related to a therapeutic response that improved capacity for response inhibition, re-evaluation of threat, and memory encoding and retrieval.

While the function to structure directional cross-modal brain relationship remains speculative, recent work in CHR-P tentatively supports this notion. Schobel and colleagues (2013) observed hypermetabolism in the CA1 subfield of the hippocampus in CHR-P prior to psychosis onset and reductions in HV. Hypermetabolism is related to FC, at least in part, as fMRI BOLD signal captures a metric of metabolic demand related to the deoxygenation of hemoglobin at active brain areas. In addition, reductions in CA1 subfield volume is the most replicated finding in HV alterations in CHR-P (Ho et al., 2017; Vargas et al., 2018). Considered together, the extant literature lends support to the notion that compensatory changes in hippocampal activation may precede volumetric reductions (Schobel et al., 2013; Magalhães et al., 2018). Longitudinal work is needed to establish temporal precedence between reductions in HV and changes in hippocampal FC, particularly as HV reductions demonstrate reversibility in clinical populations (Hou et al., 2020).

The divergent findings between IPL/TPJ connectivity in recent work, with De Marco and colleagues (2019) observing a positive association between TPJ FC and HV, and the present study observing a negative association between hippocampal-IPL FC and HV, may have implications for subsystems of the DMN. In general, the limited research in this area of cross-modal brain relationships including the hippocampus implicates a DMN subsystem including the

IPL, TPJ (De Marco et al., 2019), mPFC (Nelson et al., 2020; Liu et al., 2020), and temporal poles (Igelström et al., 2015). Moreover, the present study implicates a major hub in this DMN subsystem, including the IPL and superior temporal pole, as sensitive to changes in HV, similar to prior work which found that the PRS for SCZ is associated with reductions in HV and hippocampal-mPFC connectivity, another major hub in the DMN (Liu et al., 2020). Consistent with FC irregularities in this subsystem across the psychosis spectrum, changes in regional homogeneity (i.e., a measure of consistency of neural activity among neighboring voxels) of rsfMRI signal have been observed in the IPL and precuneus in individuals with FEP (Zhao et al., 2018), consistent with significant diagnostic group differences in connectivity between the precuneus and hippocampus in the present study, with HC demonstrating greater mean connectivity than CHR-C subjects. It is possible that the IPL and TPJ are differentially associated with changes in HV, while the IPL and superior temporal pole are differentially associated with psychosis risk.

Although diagnostic group differences detected in the present study were limited, it is worth considering their potential implications. The IPL often co-activates with the superior temporal pole (Igelström & Graziano, 2017), and the association between bilateral HV and right hippocampal connectivity with the left superior temporal pole was significantly moderated by diagnostic group in the present study. The temporal pole, located in the anterior region of the temporal lobe, has a crucial functional role in the retrieval of episodic and semantic memory and processing of emotional stimuli (Markowitsch, 1995; Grabowski et al., 2001; Sugiura et al., 2001). Prior investigations of temporal gray matter have found that the volume of the left temporal pole is significantly correlated with the volume of the left anterior amygdala-hippocampal complex (Kasai et al., 2003), and the volumes of subdivisions of the temporal pole

have been shown to correlate with the severity of psychotic symptoms (Takahashi et al., 2006), further implicating zones of this DMN subsystem as vulnerable to structural changes within the network possibly due to psychosis and environmental stress. While speculative, it is possible that alterations in temporal pole FC with the hippocampus are present in CHR-P before reductions in temporal gray matter are observed. Reduced left temporal gray matter is a morphological feature of psychosis and related disorders, including hospitalized individuals with FEP (Kasai et al., 2003), schizotypal personality disorder (Takahashi et al., 2006), and chronic SCZ (Wright et al., 1999; Gur et al., 2000; Rajarethinam et al., 2000). Unpacking the significant interaction term between right hippocampal-left superior temporal pole FC and bilateral HV in the present study revealed a positive cross-modal relation in CHR-P, consistent with the hypothesis that reductions in HV would be positively associated with hippocampal FC. In contrast, the negative association between bilateral HV and FC between the right hippocampus and left temporal pole in HC in this study may suggest that, in the absence of a psychosis risk syndrome or disorder, reductions in HV are associated with greater recruitment of the temporal pole, perhaps reflecting greater recruitment of brain areas subserving different types of memory or other compensatory processes. This notion is consistent with the differences observed in direction and magnitude of the relation between HV and hippocampal FC between diagnostic groups in the present study (Figures 2–5).

Findings of the present study also provide modest support for left lateralized abnormalities in psychosis (see Shenton et al., 2001 for a review), as all nominally significant findings across regression models (with exception of significant associations between the right hippocampus and bilateral IPL in prediction of right HV) included left hippocampal FC, left HV, or both, with a preponderance of associations with the IPL. The IPL exhibits left greater than

right asymmetry, a pattern considered important for normal brain development, so it is perhaps unsurprising that structural changes to the hippocampus and their association with IPL connectivity would follow left greater than right asymmetries as well. Specifically, in each model including left-side HV or connectivity in the present sample (i.e., left ipsilateral, left contralateral, and right contralateral), hippocampal FC accounted for approximately 2% of the variance in HV. In the right ipsilateral model, right hippocampal FC accounted for only 0.2% of the variance in right HV.

There are several limitations to the present study. First, it is limited by the use of a static, mean connectivity ROI analysis. Although there is strong theoretical backing for selecting the hippocampus as a seed ROI in investigations of cross-modal brain relationships (Sullivan et al., 2001; Peper et al., 2007; Kremen et al., 2010), seed-based ROI analyses are highly influenced by the position of the seed (Igelström & Graziano, 2017). Alternative approaches, such as independent components analysis (ICA) or eigenvector centrality mapping, are an appropriate next step for this work as such approaches isolate spatiotemporally consistent components of BOLD signal in a data-driven fashion to model coherent brain networks. Such work will be important to elucidate patterns of compensatory changes in hippocampal FC related to the multiple brain networks in which the hippocampus is involved. Moreover, local ICA, which enhances the spatial sensitivity of hubs and clusters (Igelström et al, 2015), may enhance identification of functional changes within the IPL (or another major hub, such as the mPFC) sensitive to changes in HV and elucidate the organization of this hub (e.g., related to the TPJ and temporal poles). Dynamic rsfMRI approaches (Damaraju et al., 2014) may also be considered to capture real-time fluctuations in network coherence (e.g., capturing a connectivity matrix for every 30 seconds during acquisition rather than averaging connectivity across the entire

acquisition period) and assess how between- and within-network dynamics may be related to brain structural changes.

Other measures of stress reactivity, including levels of endogenous glucocorticoids, should also be considered in future work to assess their potential moderating role in cross-modal brain relationships. In investigations of psychosis and CHR-P, interactions with diagnostic group should be considered given observed differences in the cortisol response across the psychosis spectrum. An adequate cortisol response is considered a marker of an adaptive stress response (Reinelt et al., 2019); however, dysregulation of the HPA axis in psychosis and at-risk populations is supported by evidence including elevated basal cortisol in both FEP (Cohrs et al., 2006) and CHR-P (Walker et al., 2010; Walker et al., 2013). At the same time, studies of the cortisol awakening response, which is partially independent of baseline levels, have described a blunted cortisol response in CHR-P, FEP, and individuals at familial high-risk for SCZ (Mondelli et al., 2010; Day et al., 2014; Cullen et al., 2014), and there is evidence of blunting of the cortisol response to laboratory stressors in FEP and SCZ (Jansen et al, 2000; van Venrooji et al., 2010).

Consistent with prior work (De Marco et al., 2019; Liu et al., 2020), the present study largely implicates the DMN subsystem including the IPL, TPJ, superior temporal pole, and mPFC (Igelström et al., 2015) in changes in HV. Specific findings related to the IPL and thalamus may suggest that, under certain conditions, the DMN is organized to optimally distribute metabolic resources to brain areas which support diverse functions including perception, information processing, working memory, and response inhibition (Igelström & Graziano, 2017; Reinelt et al., 2019). Future work investigating hippocampal cross-modal brain relationships should consider segmenting the hippocampus into its anterior and posterior

portions, or by subfield, to provide greater specificity in elucidating how structural changes to the hippocampus are associated with functional connectivity between nodes of distributed brain networks.

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Table 1. Demographic Characteristics

Characteristic	HC (n = 143)	CHR-NC (n = 218)	CHR-C (n = 28)	Statistical Test for Significance (2-Tailed)	*P* value	Post Hoc Tukey Test
Age, mean (SD)	19.8 (4.5)	18.9 (3.9)	18.3 (4.0)	$F = 2.8$	.06	NA
Male sex, No. (%)	79 (56)	129 (58.6)	17 (60.7)	$\chi^2 = .34$	.84	NA
Education level, mean (SD)	12.7 (3.4)	11.7 (2.7)	11.1 (2.6)	$F = 7.1$	**< .001**	HC > CHR-NC, CHR-C
Paternal education score, mean (SD)	6.5 (1.8)	6.4 (1.7)	6.0 (1.8)	$F = .91$	.40	NA
Maternal education score, mean (SD)	6.8 (1.6)	6.3 (1.5)	6.9 (1.9)	$F = 4.6$	**.01**	HC > CHR-NC
Race/ethnicity, No. (%)						
White	72 (51.1)	130 (59.1)	14 (50)	$\chi^2 = 2.6$	.27	NA
Hispanic or Latino	23 (16.3)	43 (19.5)	4 (14.3)	$\chi^2 = .89$	.64	NA
Black	33 (23.4)	35 (15.9)	6 (21.4)	$\chi^2 = 3.2$	.20	NA
Asian	16 (11.3)	13 (5.9)	3 (10.7)	$\chi^2 = 3.6$	.16	NA
First Nations	2 (1.4)	4 (1.8)	0 (0)	$\chi^2 = .56$	.76	NA
Interracial	11 (7.8)	27 (12.3)	4 (14.3)	$\chi^2 = 2.2$	.34	NA

Table 2. One-way Analysis of Variance (ANOVA) examining diagnostic-group differences in bilateral HV and FC with other nodes of the default mode network (DMN)

	Right Hippocampal		**Left Hippocampal**	
Outcome	**F statistic**	***P* value**	**F statistic**	***P* value**
L med sup front	$F(2, 386) = .61$	.55	$F(2, 386) = .02$	.98
R med sup front	$F(2, 386) = .01$	.98	$F(2, 386) = .63$	.53
L orb med front	$F(2, 386) = .77$	.46	$F(2, 386) = 2.30$	.10
R orb med front	$F(2, 386) = .35$	.71	$F(2, 386) = 1.04$	.36
L ACC	$F(2, 386) = .33$	.72	$F(2, 386) = .36$	.70
R ACC	$F(2, 386) = .24$	.78	$F(2, 386) = .67$	.51
L PCC	$F(2, 386) = .86$	.43	$F(2, 386) = .22$	.80
R PCC	$F(2, 386) = .79$	.46	$F(2, 386) = .41$	.66
L parahipp gyr	$F(2, 386) = .40$	.67	$F(2, 386) = .14$	.87
R parahipp gyr	$F(2, 386) = 1.76$	.17	$F(2, 386) = .37$	.69
L inf parietal	$F(2, 386) = .22$	.81	$F(2, 386) = 1.80$	.17
R inf parietal	$F(2, 386) = .47$	.62	$F(2, 386) = 2.42$	.09
L angular gyr	$F(2, 386) = 2.17$	.12	$F(2, 386) = 1.51$	.22
R angular gyr	$F(2, 386) = 1.24$	.29	$F(2, 386) = 2.52$	.08
L precuneus	$F(2, 386) = .27$	.77	**$F(2, 386) = 3.37$**	**.04**
R precuneus	$F(2, 386) = .77$	.47	**$F(2, 386) = 2.95$**	**.05**
L caudate	$F(2, 386) = 1.45$	.24	$F(2, 386) = .99$	.37
R caudate	$F(2, 386) = .79$	.45	$F(2, 386) = .63$	.54
L putamen	$F(2, 386) = 1.33$	.27	$F(2, 386) = .39$	.67
R putamen	$F(2, 386) = 1.86$	.16	$F(2, 386) = .80$	.45
L thalamus	$F(2, 386) = .79$	.46	$F(2, 386) = .47$	.63
R thalamus	$F(2, 386) = .33$	.72	$F(2, 386) = 1.11$	.33
L sup temp pole	$F(2, 386) = .13$	.88	$F(2, 386) = .06$	.94
R sup temp pole	$F(2, 386) = .90$	.41	$F(2, 386) = .55$	.58
L mid temp	$F(2, 386) = .29$	.75	$F(2, 386) = .18$	.84
R mid temp	$F(2, 386) = .09$	.92	$F(2, 386) = .38$	.69
L mid temp pole	$F(2, 386) = .28$	.76	$F(2, 386) = .45$	.64
R mid temp pole	$F(2, 386) = .69$	.50	$F(2, 386) = .82$	.44
Volume	$F(2, 386) = 1.26$	.29	$F(2, 386) = .22$	.80

Table 3. Results of nominally significant tests from matrix regression, $p < .05$, with bias-corrected 95% confidence intervals from bootstrapping methods

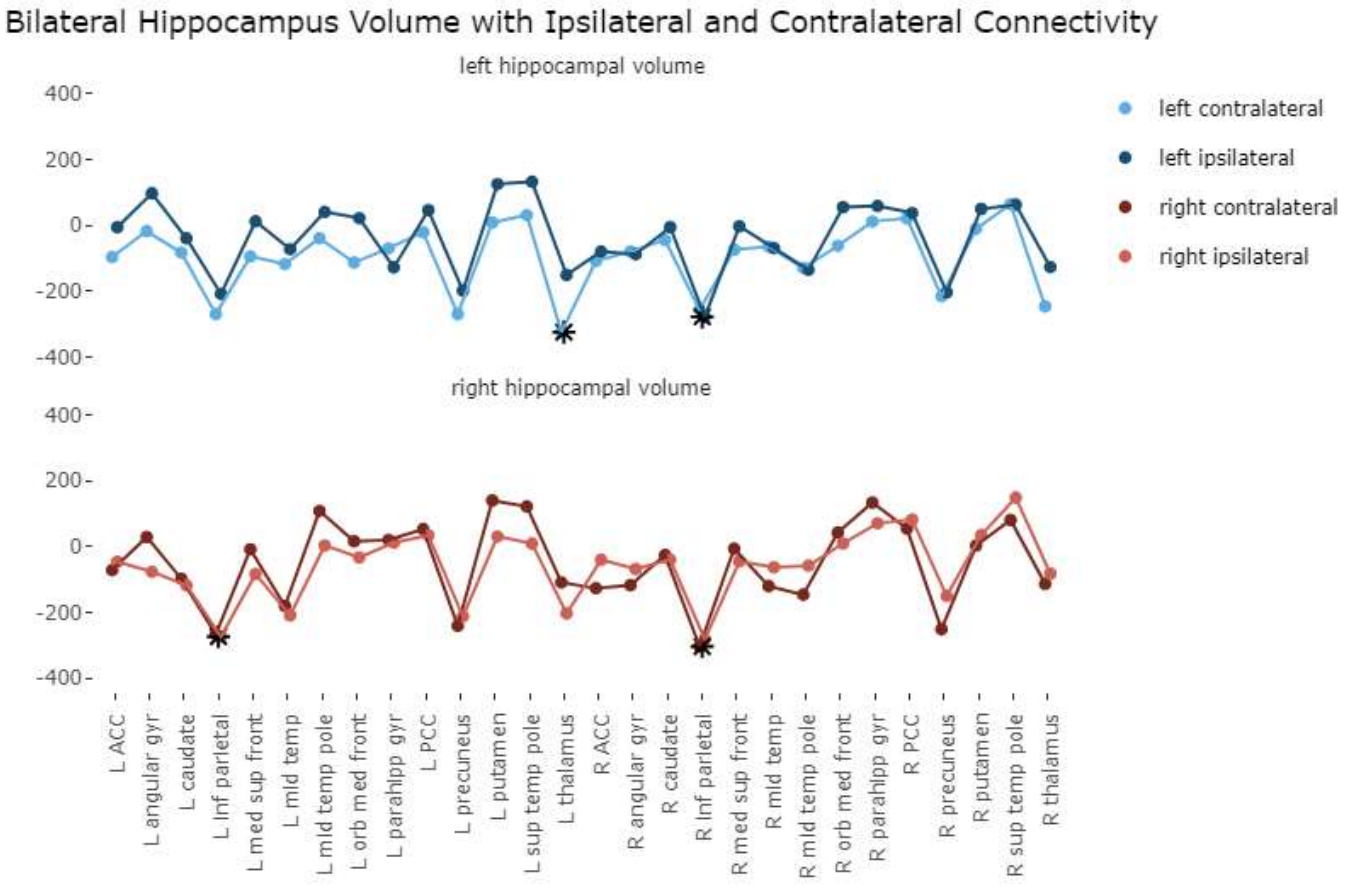
					95% CI		
Version	Node	Estimate	SE	*t* statistic	LL	UL	*p* value
Left ipsilateral	**R inf parietal**	**- 277.99**	**128.60**	**- 2.16**	**- 529.76**	**- 23.68**	**0.031**
Left contralateral	L inf parietal	- 270.11	129.78	- 2.08	- 525.56	- 17.65	0.038
Left contralateral	L precuneus	- 270.31	125.50	- 2.15	- 522.83	- 23.69	0.032
Left contralateral	**L thalamus**	**- 324.61**	**131.85**	**- 2.46**	**- 580.27**	**- 64.00**	**0.014**
Right contralateral	L inf parietal	- 266.25	122.17	- 2.18	- 501.44	- 28.67	0.030
Right contralateral	**R inf parietal**	**- 303.04**	**122.98**	**- 2.46**	**- 545.13**	**- 52.13**	**0.014**
Right contralateral	L precuneus	- 240.60	119.87	- 2.01	- 477.17	- 6.27	0.045
Right contralateral	R precuneus	- 250.78	120.03	- 2.09	- 491.09	- 21.68	0.037
Right ipsilateral	L inf parietal	- 273.07	124.25	- 2.20	- 513.33	- 28.44	0.029
Right ipsilateral	**R inf parietal**	**- 281.51**	**128.47**	**- 2.19**	**- 530.99**	**- 25.51**	**0.029**

Left contralateral = left HV and right hippocampal FC; *left ipsilateral* = left HV and left hippocampal FC*; right contralateral* = right HV and left hippocampal FC; *right ipsilateral* = right HV and right hippocampal FC

Table 4. Results of simple regression between right hippocampal-left superior temporal pole connectivity and bilateral hippocampal volume (HV), conducted separately by diagnostic group and hemisphere

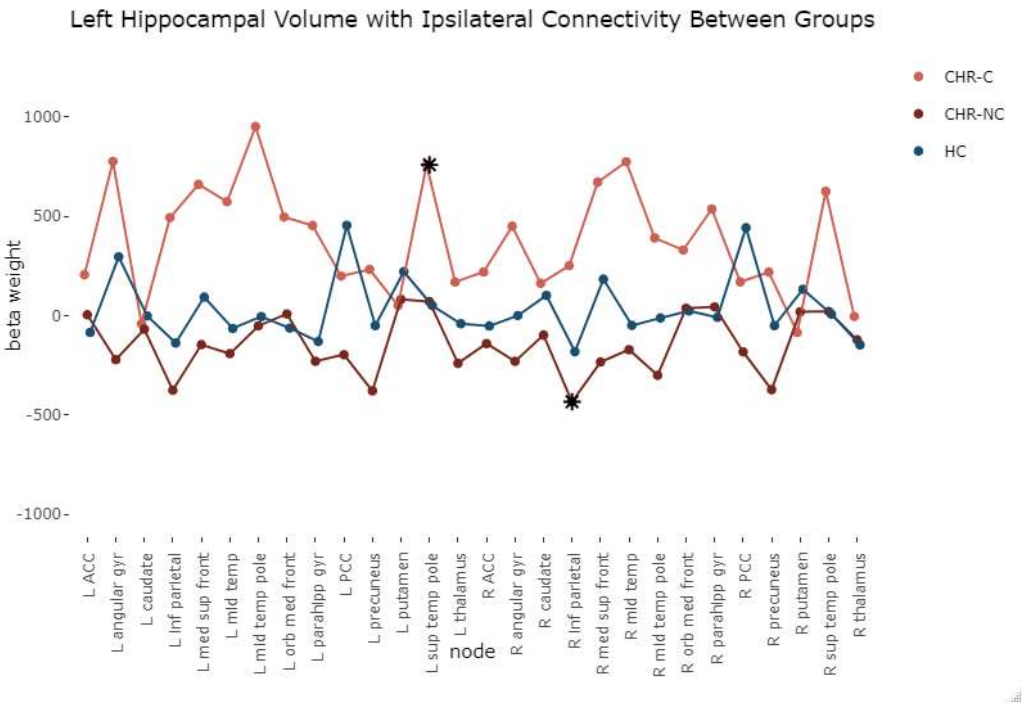
Group	Hemisphere	Estimate	SE	*t* statistic	*p* value
Control	Left HV	- 339.59	185.29	- 1.83	0.069
CHR-NC	Left HV	227.07	186.62	1.22	0.225
CHR-C	Left HV	630.39	366.54	1.72	0.101
Control	Right HV	- 285.96	170.19	- 1.68	0.095
CHR-NC	Right HV	181.18	181.16	1.00	0.318
CHR-C	Right HV	367.23	388.46	0.95	0.353

Figure 1. Associations between bilateral hippocampal functional connectivity and bilateral HV, separately by hemisphere, for each major node of the default mode network



*significant after correcting for multiple comparisons.
Left contralateral = left HV and right hippocampal FC; *left ipsilateral* = left HV and left hippocampal FC; *right contralateral* = right HV and left hippocampal FC; *right ipsilateral* = right HV and right hippocampal FC.

Figure 2



*significant after correcting for multiple comparisons

Figure 3

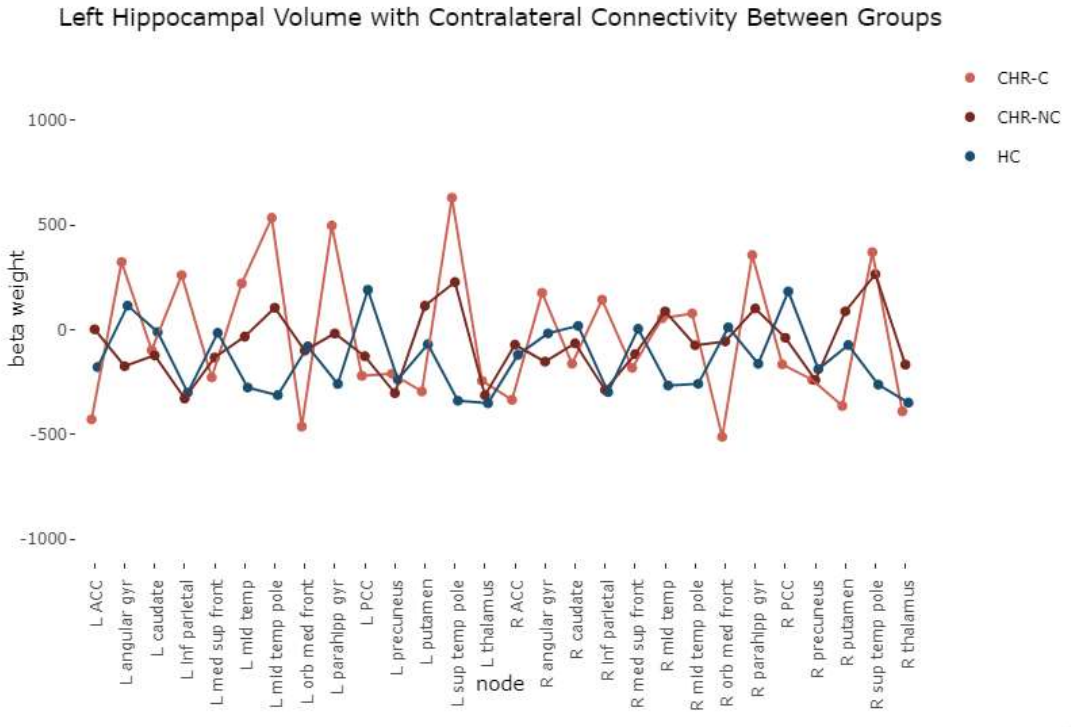
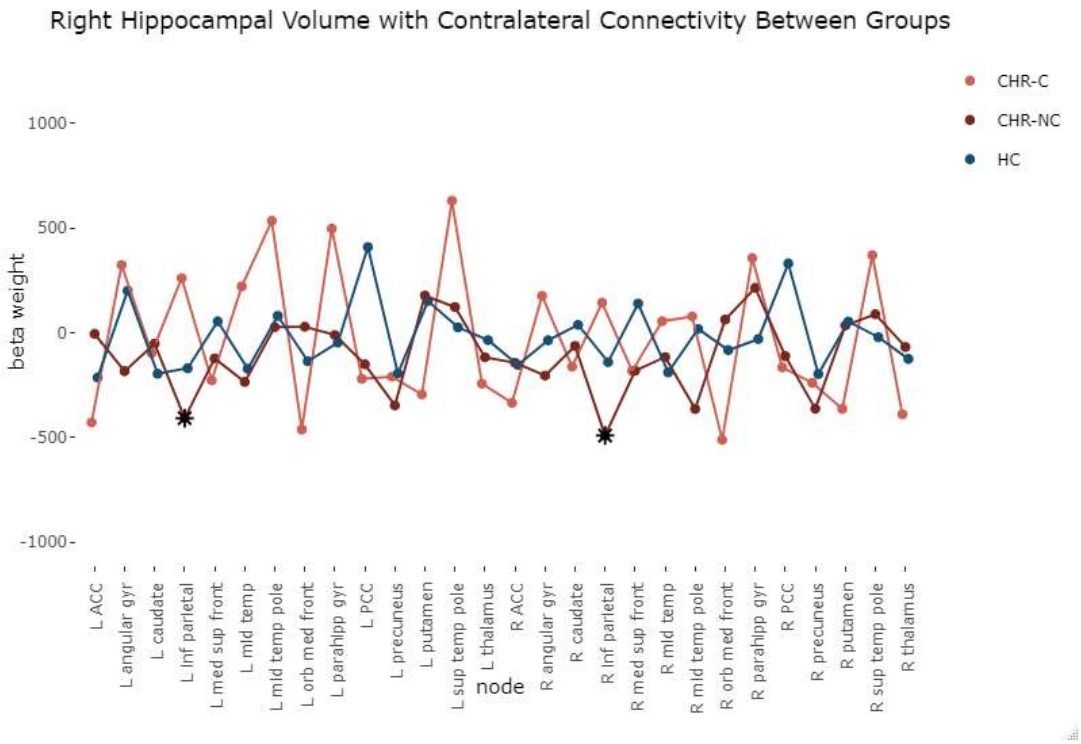
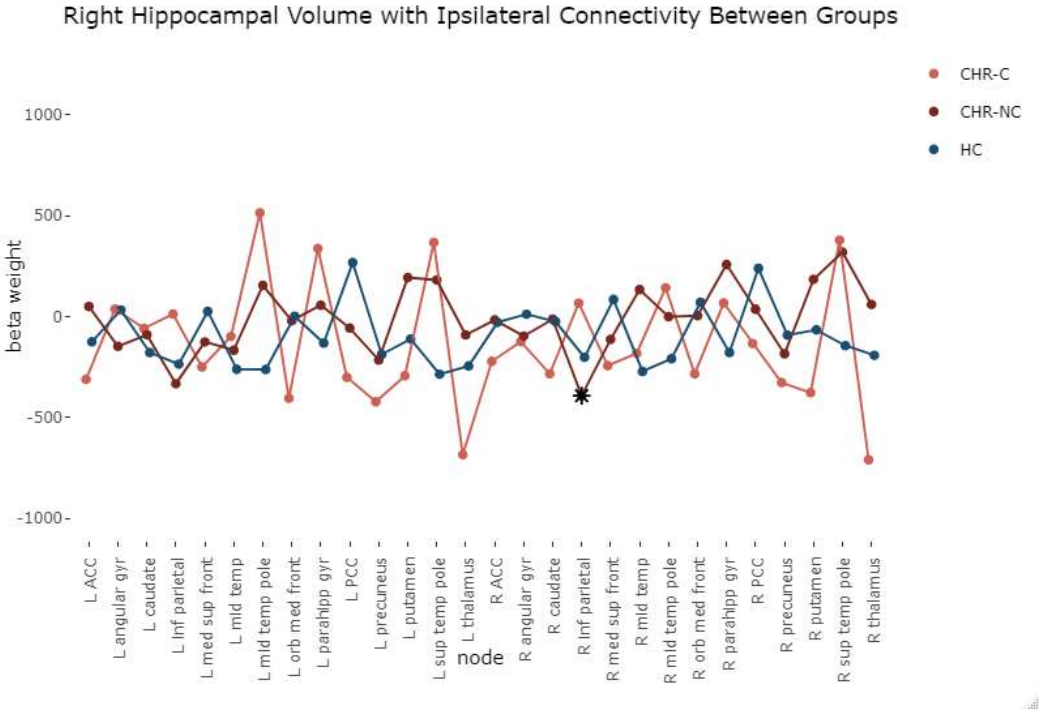


Figure 4



*significant after correcting for multiple comparisons

Figure 5



*significant after correcting for multiple comparisons

Figure 6

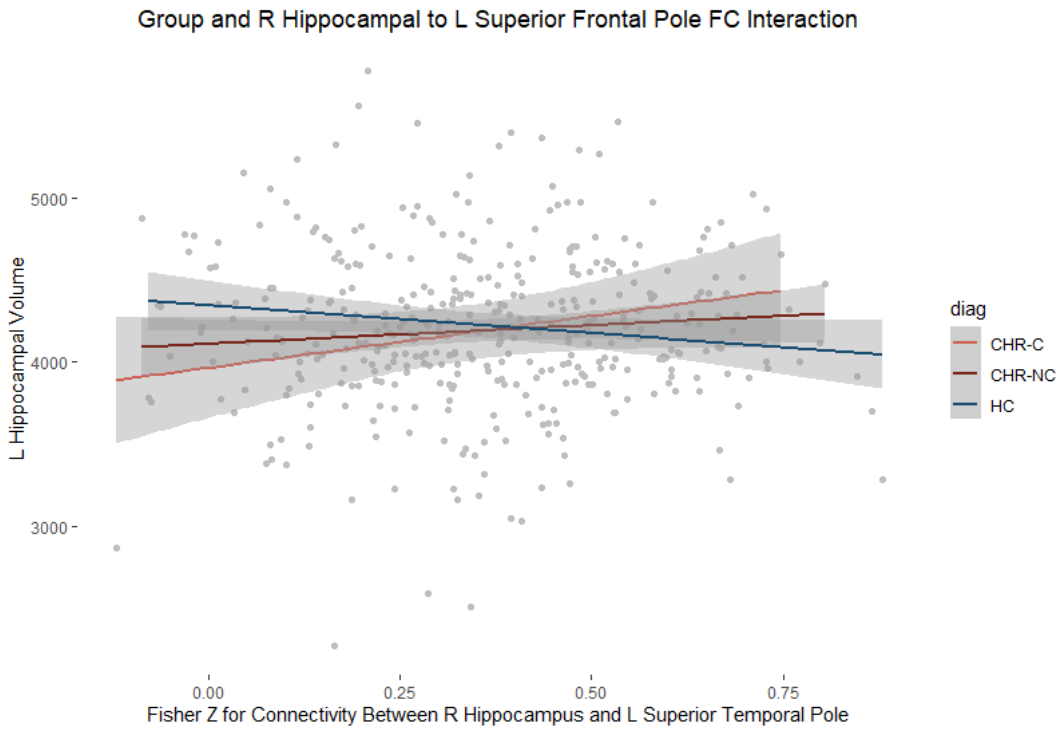


Figure 7