Brain Network Connectivity–Behavioral Relationships Exhibit Trait-Like Properties: Evidence From Hippocampal Connectivity and Memory

Alexandra Touroutoglou,[1,2,3†] Joseph M. Andreano,[2,3†] Lisa Feldman Barrett,[2,3,4‡] and Bradford C. Dickerson[2,3,5‡]*

ABSTRACT: Despite a growing number of studies showing relationships between behavior and resting-state functional MRI measures of large-scale brain network connectivity, no study to our knowledge has sought to investigate whether intrinsic connectivity–behavioral relationships are stable over time. In this study, we investigated the stability of such brain–behavior relationships at two timepoints, approximately 1 week apart. We focused on the relationship between the strength of hippocampal connectivity to posterior cingulate cortex and episodic memory performance. Our results showed that this relationship is stable across samples of a different age and reliable over two points in time. These findings provide the first evidence that the relationship between large-scale intrinsic network connectivity and episodic memory performance is a stable characteristic that varies between individuals. © 2015 Wiley Periodicals, Inc.

KEY WORDS: resting-state fMRI; hippocampus; individual differences; reliability; memory

[1] Department of Neurology, Massachusetts General Hospital and Harvard Medical School, 149 13th St., Charlestown, Massachusetts; [2] Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, 149 13th St., Charlestown, Massachusetts; [3] Psychiatric Neuroimaging Division, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, 149 13th St., Charlestown, Massachusetts; [4] Department of Psychology, Northeastern University, Boston, Massachusetts; [5] Frontotemporal Disorders Unit, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, 149 13th St., Charlestown, Massachusetts
[†] A.T. and J.M.A. made equivalent contributions and share first authorship.
[‡] L.F.B. and B.C.D. made equivalent contributions and share senior authorship.
*Correspondence to: B.C. Dickerson, MGH Frontotemporal Disorders Unit, 149 13th St., Suite 2691, Charlestown, MA 02129. E-mail: bradd@nmr.mgh.harvard.edu

INTRODUCTION

The brain is intrinsically organized into large-scale distributed functional networks, measureable in living individuals using resting-state functional connectivity MRI (fcMRI) (Biswal et al., 1995; Greicius et al., 2003; Smith et al., 2009; Yeo et al., 2011), among other imaging methods. A growing body of literature focuses on how individual differences in the strength of intrinsic connectivity of these networks relate to individual differences in a variety of experiences and behaviors such as in motor function (Fox et al., 2007), learning (Supekar et al., 2013; Ventura-Campos et al., 2013), working memory (Hampson et al., 2006), episodic memory (Wang et al., 2010a; Wang et al., 2010b), intelligence (van den Heuvel et al., 2009), executive function (Gordon et al., 2015; Seeley et al., 2007; Touroutoglou et al., 2012), social behaviors (Bickart et al., 2012; Di Martino et al., 2009), and affective experiences (Seeley et al., 2007; Touroutoglou et al., 2012; van Marle et al., 2010) as well as personality traits (Fulwiler et al., 2012; LaBar et al., 2001). Intrinsic connectivity differences have also been proposed as biomarkers for various neuropsychiatric disorders (Fox and Greicius, 2010; Greicius, 2008; Menon, 2011; Zhang and Raichle, 2010).

The growing evidence that fcMRI measures of large-scale neural network connectivity predict a range of normal human behavior raises a critically important question: to what extent are these brain–behavior relationships stable over time (i.e., can they be considered trait-like) vs. how much do they fluctuate from one scanning/testing session to the next (i.e., should they be considered state-like)? This raises further questions about the reliability of intrinsic connectivity network measures, studies of which have typically shown moderately high reliability (Braun et al., 2012; Guo et al., 2012; Shehzad et al., 2009; Song et al., 2012; Van Dijk et al., 2010; Zuo et al., 2010) on the network level. Other data show, however, that intrinsic connectivity networks can be dynamic (Hutchison et al., 2013), with recent task-evoked cognitive (Albert et al., 2009; Waites et al., 2005), and affective states (Harrison et al., 2008) or even task-free states of previous runs within the same resting-state scan session

(Van Dijk et al., 2010) influencing connectivity strength, particularly in individual pairwise correlations between brain regions. Thus, fMRI-derived intrinsic connectivity measures are thought to reflect a combination of stable and transient influences (Buckner, 2010; Buckner et al., 2013; Deco et al., 2010).

Despite the optimistic results of initial resting-state reliability studies, no study to our knowledge has sought to investigate whether the relation between intrinsic connectivity and behavioral measures are stable over time. In this study, we used a strong *a priori* hypothesis-driven approach and investigated the stability of the relationship between the strength of hippocampal connectivity to posterior/precuneus cortex (PCC) and episodic memory performance, a finding previously reported by our laboratory in Wang et al. (2010a). We analyzed behavioral and scan data collected at two timepoints approximately 1 week apart. We hypothesized that the same relationship observed in Wang et al. (2010a)'s study would generalize to a sample of new participants of a different age, and further that the relationship within our sample would be reliable over two points in time. Support for this hypothesis would provide evidence that the relationship between hippocampal connectivity and episodic memory performance is a stable trait that varies between individuals.

MATERIALS AND METHODS

Participants

Forty adults ranging in age from 18 to 54 (mean age = 27.97, SD = 9.60; 23 females) participated in this study, which involved the collection of resting-state blood oxygenation-level-dependent (BOLD) data as well as task-evoked BOLD data. All participants were right-handed, native English speakers and had normal or corrected-to-normal vision. No participant reported a history of neurological or psychiatric disorders.

Behavioral Data Acquisition: Encoding and Retrieval Tasks

Participants completed in the scanner an associative memory encoding task followed by a retrieval memory task for two timepoints, approximately 1 week apart. During the first scan session, following resting-state scans, participants were engaged in an affective task unrelated to the analyses of this study and then completed the associative memory encoding task. The affective task was part of a larger study examining the aging effects on affect and memory and included 9 high arousal, negative valence IAPS slides (arousal – mean = 5.73, SD = 0.81, valence – mean = 2.718, SD = 0.7) presented for 6 s each in order to induce negative affect. After the first round of induction, participants then began an associative memory encoding task. On each of 80 trials, participants were presented with a neutral image or scene as well as a common word selected from the Medical Research Council Psycholinguistic Database

(Coltheart, 1981). Each image/word pair was presented for 6 s, and a total of 20 pairs were encoded in a single run. To ensure depth of encoding, participants were asked to judge whether the word "matched" the picture. As picture/word pairs were created randomly, and pairs with an obvious semantic connection were excluded, this judgment was subjective. Next, participants completed a second affect induction and a second run of associative encoding, followed by two more induction and encoding runs, for a total of four runs each.

A retention delay of approximately 10 min followed, during which other scans unrelated to these analyses were performed. After this delay, recognition testing began. Participants were presented with all 80 pairs learned during encoding, as well as 40 pairs made up of new words and pictures, and 40 rearranged pairs made of words and pictures seen previously, but not previously associated. Each picture was presented for 6 s, during which time the participant responded by button press whether the pair had appeared during encoding, or whether it was a new or rearranged pair (yes/no).

Approximately 1 week later, the second scan session was performed. Participants returned and underwent an identical procedure with two differences: (1) neutral, rather than negative, affect was induced during induction runs through the presentation of low arousal, neutral valence IAPS images (arousal − mean = 3.3, SD = 0.9, valence − mean = 5.39, SD = 0.76), and (2) a new set of words and images were used during encoding and retrieval.

Each recognition trial was coded as a hit, miss, false alarm, or correct rejection, and recognition accuracy was computed in terms of d', a measure which controls for individual response bias ($d' = z(FA)-z(hits)$). Thus, for each subject, the memory measure were d' Timepoint 1 (d' under negative induction condition) and d' Timepoint 2 (d' under neutral induction condition). d' was then used in the subsequent analyses described below.

MRI Data Acquisition and Preprocessing

Imaging data were collected on a 3T Magnetom Tim Trio system (Siemens Medical Systems, Iselin, NJ) at Massachusetts General Hospital, equipped for echo planar imaging (EPI) with a 12-channel phased-array head coil. Head motion was minimized using head restraints, including a pillow and foam padding. Noise was attenuated with ear plugs. Structural MRI data were acquired using a T1-weighted 3D MPRAGE sequence [TR/TE/flip angle = 2530 ms/3.48 ms/7°, resolution = 1.0 mm isotropic).

Whole-brain resting-state fMRI data were acquired with echo-planar sequence [TR = 5,000 ms; TE = 30 ms; FA = 90°). These parameters allowed us to obtain 55 slices and have a spatial resolution of 2.0 mm isotropic voxels. The resting state scan was 6.40 min long and the data involved one run of 76.8 time points. During all resting-state fMRI runs, participants were directed to keep their eyes open without fixating and to remain as still as possible. Resting-state fMRI runs preceded the task-based fMRI runs.

Preprocessing of the resting-state fMRI data involved a series of previously established resting-state functional connectivity MRI (rs-fcMRI) procedures (Biswal et al., 1995; Van Dijk et al., 2010; Vincent et al., 2007). After removing the first four functional volumes, the following steps were completed: correction for slice-dependent time shifts (SPM2, Wellcome Department of Cognitive Neurology, London, United Kingdom), correction for head motion with rigid-body transformation in three translation and three rotations (FMRIB, Oxford, UK), spatial normalization to Montreal Neurological Institute (MNI) atlas space, resampling to 2 mm isotropic voxels, spatial smoothing using a 6 mm full-width at half-maximum (FWHM) Gaussian kernel, and temporal band-pass filtering to remove frequencies > 0.08 Hz. We then removed sources of spurious variance and their temporal derivatives from the data through linear regression (six parameters derived from the rigid-body head motion correction, the signal averaged over a region within the deep white matter, and the signal averaged over the ventricles) and the residual BOLD time course was retained for functional connectivity analysis. In addition to these factors, we regressed out the signal averaged over the whole brain, as it has been suggested (Fox et al., 2009; Weissenbacher et al., 2009) that the use of global signal regression in brain systems expected to show positive correlations [such as the hippocampal connectivity to PCC (Van Dijk et al., 2010; Vincent et al., 2008; Wang et al., 2010a)] reduces certain elements of noise related to false positives.

Resting-State fMRI Analysis

To examine the intrinsic functional connectivity strength between the hippocampus and PCC, we used seed-based rs-fcMRI analysis. A hypothesis-driven approach was taken for this analysis, creating spherical regions of interest (ROIs) (4 mm radius) around hippocampal formation (right hippocampus coordinates: $+21, -6, -18$, MNI) and PCC bilaterally (right PCC coordinates: $+3, -51, 39$ and left PCC coordinates: $-9, -54, 39$, MNI). The coordinates of these seeds were determined from the results of a previous study by our laboratory (Wang et al., 2010a) that examined the relationship between hippocampal intrinsic connectivity and episodic memory performance (Fig. 1). In that study, peak activations in a contrast comparing encoding activity for subsequently remembered items vs. fixation were found in the right and left hippocampi. Additionally, a contrast comparing fixation vs. subsequently remembered items showed peak activations in PCC bilaterally. The strength of connectivity between each pair of these task-defined ROIs was then tested for correlation with each participants' overall memory performance. The authors showed significant correlations between episodic memory performance and connectivity in the right hippocampus and bilateral PCC ROIs (Fig. 1). These ROIs were used as seeds in the functional connectivity analysis of this study.

To examine the intrinsic functional connectivity of the right hippocampus and bilateral PCC seeds, we computed Pearson's product moment correlations, r, between the mean signal time
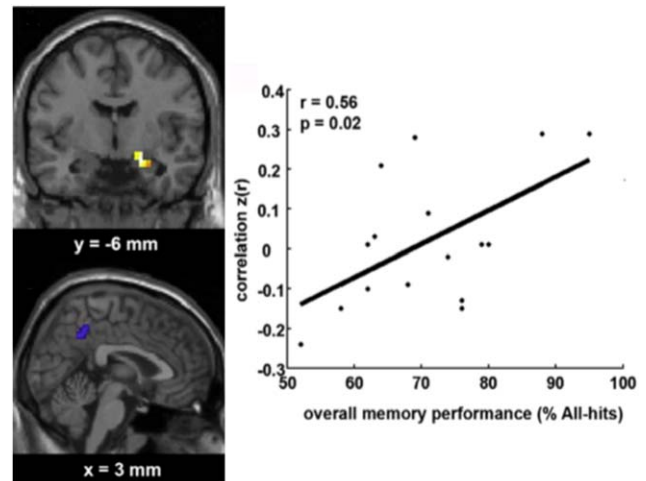

FIGURE 1. Hippocampus - PCC connectivity significantly predicted episodic memory performance in an independent sample previously published by our laboratory (Wang et al., 2010a). In that study, a contrast comparing high confidence hits vs. fixation identified clusters containing hippocampi activation peaks (left, top) and a contrast comparing fixation vs. high confidence hits identified clusters containing PCC deactivations (left, bottom). Wang et al. (2010a) then used these task-based ROIs as seed ROIs in a subsequent resting state functional connectivity analysis. The strength of intrinsic connectivity between the right hippocampal ROI and right PCC ROI (scatter plot on the right) predicted overall memory performance in their sample of older adults. Figure adapted from Wang et al. (2010a). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

course of the hippocampus and bilateral PCC. Fisher's r-to-z correlation coefficients were then calculated between each pair of hippocampus-PCC ROIs. The averaged pairwise connectivity measure of $z(r)$ values of the right hippocampus to left PCC and the right hippocampus to right PCC was used for the stability analyses of the brain–behavioral relationships.

Stability of Memory Performance and Hippocampal Connectivity

To assess the stability of memory performance, we computed intraclass correlation coefficients (ICC) (two-way random effects with absolute agreement) between memory performance at Timepoint 1 and memory performance at Timepoint 2. The Pearson's product moment correlations, r, of memory performance at Timepoint 1 (d') with memory performance at Timepoint 2 (d') were also calculated and the relationship between memory performance at these timepoints was displayed in scatterplots.

Correspondingly, to assess the reliability of the strength of connectivity of the hippocampal connectivity, we computed intraclass correlation coefficients (ICC) (two-way random effects with absolute agreement) between the $z(r)$ values of the right hippocampus to PCC at Timepoint 1 and the $z(r)$ values of the right hippocampus to PCC at Timepoint 2. The Pearson's product moment correlations, r, of hippocampal connectivity to PCC at Timepoint 1 with hippocampal connectivity
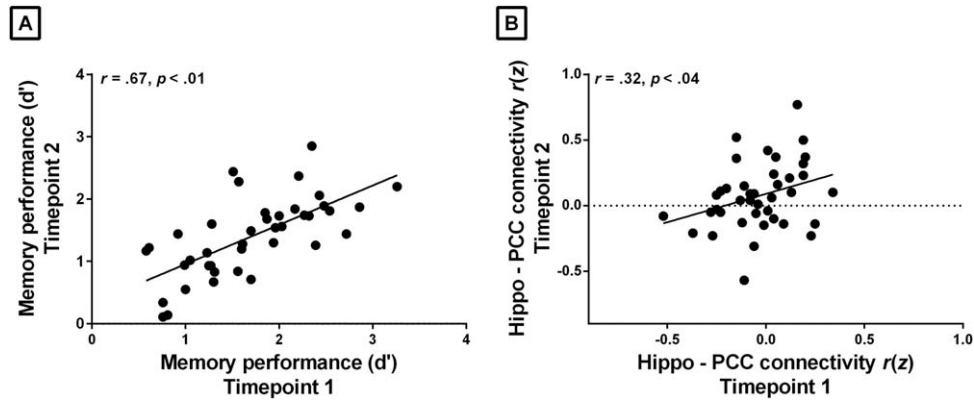
FIGURE 2.   Stability of memory performance and hippocampal connectivity to PCC (Hippo - PCC). (A) Recognition discriminability memory performance (*d'*) was highly stable across Timepoint 1 and 2 (*r* = 0.67, *p* <0.01). (B) The relationship between the hippocampal connectivity to PCC between Timepoint 1 and Timepoint 2 (*z*-transformed correlation coefficients computed by correlating the spontaneous activity between the right hippocampus and bilateral PPC) was relatively weak across the two sessions (*r* = 0.32, *p* = 0.04).

to PCC at Timepoint 2 were also computed and the relationship between the hippocampal connectivity at these timepoints was displayed in scatterplots. All analyses were conducted using PASW Statistics 21, Release Version 21.0.0 (SPSS, Inc., 2009, Chicago, IL, www.spss.com). Results were considered statistically significant at $p < 0.05$.

Stability of the Brain–Behavior Relationship

We examined the relationship between hippocampal connectivity to PCC and memory performance, using a series of linear regression analyses. We conducted a linear regression analysis using hippocampal connectivity at Timepoint 1 (averaged pairwise connectivity measure of $z(r)$ values of the right hippocampus with left and right PCC) as independent variable and memory performance at Timepoint 1 (d') as the dependent variable. The same analysis was repeated for Timepoint 2.

To assess whether hippocampal connectivity at either timepoint predicts memory performance during the other timepoint, we conducted a linear regression analysis using hippocampal connectivity at one timepoint (e.g., Timepoint 1) as independent variable and memory performance at the other timepoint (e.g., Timepoint 2) as the dependent variable. Brain–behavior analyses were conducted using PASW Statistics 21, Release Version 21.0.0 (SPSS, Inc., 2009, Chicago, IL, www.spss.com). Results were considered statistically significant at $p < 0.05$.

RESULTS

Consistent with prior evidence (Braun et al., 2012; Zuo et al., 2010), our reliability analyses revealed that the hippocampal intrinsic connectivity between the two timepoints (approximately 1 week apart) was moderately reliable with ICC = 0.47. A scatterplot displaying the relationship of the hippocampal

intrinsic connectivity across the two sessions ($r = 0.32$, $p < 0.04$) is shown in Figure 2 (for comparison of reliability of the connectivity across the entire default mode network, to which the hippocampus-PCC connection belongs, and within the PCC and medial prefrontal nodes of the network, see Supporting Information). Contrary to the moderate stability of the hippocampal intrinsic connectivity, episodic memory performance was highly stable across the two timepoints with ICC = 0.80. Figure 2 shows the relationship between memory performance at two timepoints ($r = 0.67$, $p < 0.01$).

Using linear regression analysis, we found that hippocampal connectivity to PCC was reliably associated with memory performance (d') at both Timepoint 1 and Timepoint 2 ($r = 0.34$, $p < 0.03$ and $r = 0.38$, $p < 0.02$, respectively) (Fig. 3 and Table 1) (for comparison of the relationship between hippocampal connectivity to PCC and item and associative memory d' subscores, see Supporting Information Table 1S). The regression analysis also revealed that hippocampal connectivity to PCC at one point in time is associated with memory performance at another point in time. The strength of connectivity between hippocampus and PCC at Timepoint 1 predicted future memory performance at Timepoint 2 ($r = 0.53$, $p < 0.01$). The strength of connectivity between hippocampus and PCC at Timepoint 2 was associated with past performance in memory at Timepoint 1 ($r = 0.47$, $p < 0.01$) (Fig. 4 and Table 1) (for comparison of reliability of the relationship between memory and connectivity across the entire default mode network, and within the PCC and medial prefrontal nodes of the network, see Supporting Information Table 2S and 3S).

DISCUSSION

The present findings demonstrate a relationship between intrinsic functional connectivity and behavior that is stable over
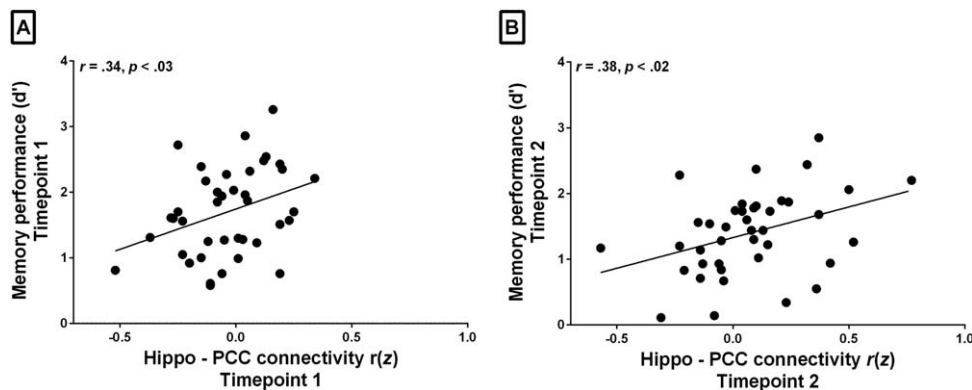
FIGURE 3. Intrinsic connectivity between the hippocampus and PCC (Hippo - PCC) predicted memory performance within sessions. The *z*-transformed correlation coefficients (*x* axis) computed by correlating the spontaneous activity between the right hippocampus and bilateral PPC ROIs reliably predicted individual recognition discriminability memory performance (*d'*, *x* axis) within a session. This relationship was consistent at two separate time points, demonstrating the reliability of this brain–behavior relationship.

time and across samples of a different age. While previous studies have related intrinsic functional connectivity measures to individual differences in performance on various cognitive tasks, it has not been clear whether brain–behavior relationships identified with intrinsic connectivity fMRI reflect stable traits, transient states, or a combination thereof. The present data provide clear evidence that such a brain–behavior relationship persists across multiple sessions. That is, intrinsic connectivity between the hippocampus and PCC predicted performance on a memory task 1 week later. Our results thus suggest that the connectivity between the hippocampus and PCC—key nodes of the large-scale default mode network, known to be involved in episodic memory (Buckner et al., 2008; Dickerson and Eichenbaum, 2010; Raichle et al., 2001)—exhibits characteristics consistent with a trait-level neurobiological measure which predicts associative memory ability, rather than a transient state.

Intrinsic functional connectivity as measured by rs-fcMRI is a heterogeneous measure, which includes persistent sources

such as anatomic connectivity and long-term changes in synaptic efficiency, temporary sources such as synaptic changes due to recent experience and state of arousal (Vaisvaser et al., 2013; Veer et al., 2011), and confounding sources such as motion, cardiac, and respiratory activity (Buckner, 2010; Buckner et al., 2013; Hutchison et al., 2013). The reliability of intrinsic connectivity observed here is comparable to the moderate levels of reliability reported in other studies. Intraclass correlation between the two timepoints was 0.40, roughly in the center of the range of reliability of networks reported in studies that have examined this question on the whole-brain level (Braun et al., 2012; Zuo et al., 2010). Previous research on the default mode network, to which the hippocampus-PCC system examined in this study belongs, has reported somewhat higher levels of reliability than we observed here (Guo et al., 2012). Our analysis also showed higher reliability of the average connectivity across the entire network, compared to the connectivity between hippocampus and PCC. It thus appears that the cortical–cortical connections between other nodes of the default

TABLE 1.

Increased Hippocampal Connectivity to PCC Predicts Better Memory Performance Within and Across Sessions (N = 40)

	Memory performance (*d'*) Timepoint 1		Memory performance (*d'*) Timepoint 2	
	B	Total R^2	*B*	Total R^2
Strength of the hippocampal intrinsic connectivity to PCC at Timepoint 1	0.34** CI: 0.12–2.3	0.12**	0.53* CI: 0.83–2.70	0.28*
Strength of the hippocampal intrinsic connectivity to PCC at Timepoint 2	0.47* CI: 0.47–1.98	0.22*	0.38** CI: 0.18–1.67	0.14**

Note. This table displays standardized regression coefficients (*B*) as well as the total variance (total R^2) in memory performance at two points in time predicted by the independent variables, each entered into a single linear regression model. Confidence interval (CI), *$p < 0.01$; **$p < 0.05$.
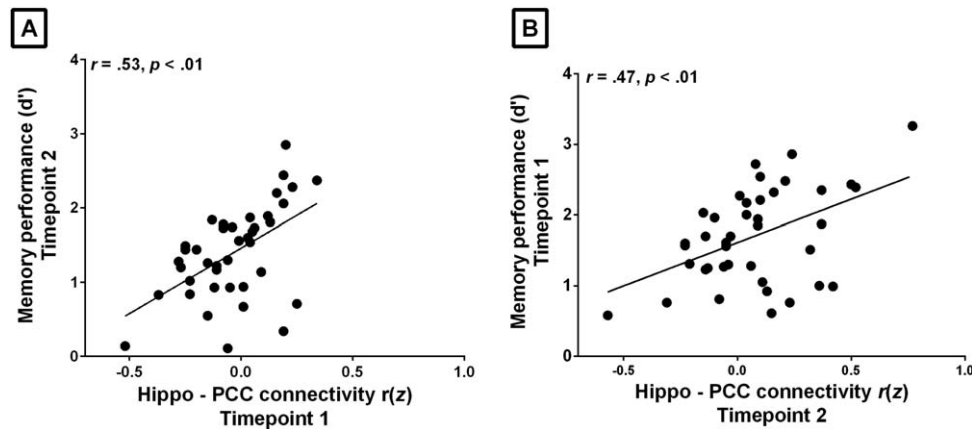
FIGURE 4. Intrinsic connectivity between the hippocampus and PCC (Hippo - PCC) predicts memory performance across sessions separated by approximately 1 week. The *z*-transformed correlation coefficients (*x* axis) computed by correlating the spontaneous activity between the right hippocampus and bilateral PPC ROIs are plotted against individual memory performance (*d′*, *x* axis) at two points in time. The strength of connectivity (A) between hippocampus and PCC at one point (Timepoint 1) predicts memory performance in the future (Timepoint 2) and (B) between hippocampus and PCC at one point in time (Timepoint 2) is associated with memory performance in the past (Timepoint 1).

mode network are comparatively more stable, than the cortical–hippocampal connections. Consistent with this view, our analysis showed that the reliability of the connection between PCC and medial prefrontal cortex—two key cortical nodes of the default mode network—was greater than the reliability of the hippocampus to PCC connection.

Yet despite the many potential sources of noise present in intrinsic functional connectivity measures, a stable within-subject signal is evident through its relationship with behavior 1 week later. Thus, although functional connectivity MRI measures obtained using the present analytic techniques appear to be only modestly reliable, the connectivity–behavior relationship described here is stable enough to be detected in the context of the variety of sources of session-level variance in the measures.

Our findings provide further support for the use of resting-state connectivity in the study of individual differences in brain–behavior relationships. Consistent with our findings, two recent studies have shown that variability in intrinsic functional connectivity predicts differences in personality traits such as agreeableness (LaBar et al., 2001; Vaisvaser et al., 2013), neuroticism, extraversion, and openness (LaBar et al., 2001). Similarly, intrinsic connectivity has been associated with variability in a wide number of behavioral domains where performance is believed to be stable, including visual and motor performance, language, learning, episodic memory, executive function, and emotional functioning (see Veer et al., 2011 for review). Evidence that resting-state connectivity can predict stable differences in personality and behavior points to its potential value as a biomarker for vulnerability to various neuropsychiatric disorders (Buckner, 2013; Fox and Greicius, 2010; Greicius, 2008; Menon, 2011; Zhang and Raichle, 2010), particularly because of the low task demands on participants. However, the utility of this method depends critically on whether intrinsic connectivity measures are stable within individuals, and are not overly influenced by state-level factors. Intrinsic connectivity has also been shown to reflect transient affective states, such as stressor-evoked anticipatory anxiety (Seeley et al., 2007) and cardiovascular reactivity (Vaisvaser et al., 2013). However, the present findings demonstrate that individual differences in resting connectivity can meaningfully predict trait-level differences in behavior despite multiple potential sources of transient variability.

One limitation of this study is that this analytic approach employed only two timepoints, approximately 1 week apart. As such, our data cannot speak to questions of reliability of resting-state fMRI data over longer time frames. Additionally, as this study focused on the relationship between episodic memory performance and hippocampal connectivity to PCC, further research will be needed to assess whether these findings generalize to relationships between more diverse behaviors and nodes of other networks. Finally, further research is needed on the sources of variance in resting-state fMRI data if we ultimately want to use measures derived from these data as markers for vulnerability to or the presence of neuropsychiatric illness.

Acknowledgments

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