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Fronto-temporal Anatomical Connectivity and Working-Relational Memory Performance Predict Everyday Functioning in Schizophrenia

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Abstract

Hippocampal (relational memory) and prefrontal cortex (PFC; working memory) impairments have been found in patients with schizophrenia (SP), possibly due to a dysfunctional connection between structures. Neuroanatomical studies that describe reduced fractional anisotropy (FA) in the uncinate fasciculus support this idea. The dysconnection hypothesis in SP was investigated by examining fronto-temporal anatomical connectivity (uncinate fasciculus FA) and PFC-hippocampal memory and their relationship with each other and everyday functioning. PFC-hippocampal memory was examined with two working-relational memory tasks: transverse patterning and virtual Morris water task. SP exhibited a performance deficit on both tasks and had

lower FA in bilateral uncinate fasciculus than healthy volunteers. Lower fronto-temporal anatomical connectivity was related to lower working-relational memory performance, and both predicted worse everyday functioning.

Keywords

schizophrenia; hippocampus; prefrontal cortex; uncinate fasciculus; transverse patterning; and connectivity

The prefrontal cortex (PFC) and hippocampus are critical for different aspects of memory function, and together play a central role in the memory impairments exhibited in patients with schizophrenia (SP; Cirillo & Seidman, 2003; Goldman-Rakic, 1994; Saykin et al., 1991; Saykin et al., 1994). The temporal lobes, particularly the hippocampi, are theorized to play an important role in the formation of long-term memory traces that relate or combine stimuli to form unique representations (Cohen & Eichenbaum, 1993; Moses & Ryan, 2006; Rudy & Sutherland, 1995). The frontal lobes are also implicated in learning and memory. The PFC, specifically the dorsolateral region, is thought to be essential for working memory, the active maintenance and utilization of information kept in mind for a short period of time (Baddeley, 2003, 1986; Goldman-Rakic, 1994; Ragland, Yoon, Minzenberg, & Carter, 2007).

Investigations into the neurological deficits found in SP have focused on specific brain structures or systems. An alternative hypothesis is that these deficits may be due to a dysfunctional connection, or “dysconnection”, between the participating brain regions (Bullmore, Frangou, & Murray, 1997; Friston, 1999, 2002; Friston & Frith, 1995). In the present context, the dysconnection hypothesis implies that there may be abnormal functional integration between PFC and hippocampus. As a result, performance deficits are expected when coordinated activity between the dorsolateral PFC and hippocampus is required in a task that involves interplay between the working and relational memory systems. Deficits on such tasks (the transverse patterning (TP) task and the Virtual Morris Water Task (VMWT)) have been observed in SP by Hanlon and collaborators (Hanlon et al., 2011; Hanlon et al., 2006; Hanlon et al., 2005).

There are different theories on how and why dysconnection between brain regions may occur in SP. Stephan and colleagues (2006; 2009) propose that the main underlying mechanism for dysconnection is abnormal NMDA receptor-mediated synaptic plasticity. They also acknowledge that irregular wiring of association fibers may affect interregional functional integration, in addition to the effects of abnormal synaptic plasticity. Bullmore et al. (1997) alternatively propose a dysplastic net hypothesis, which integrates the dysconnection hypothesis and neurodevelopmental hypothesis in schizophrenia. They describe the dysconnection of neural networks as the result of dysplastic axonal projection formation occurring in the second half of gestation. Alternatively abnormal axonal connections could occur by different means, such as disrupted myelination of axons, or elimination of axons due to neuronal death (Spoletini et al., 2009; Walterfang, Velakoulis, Whitford, & Pantelis, 2011). Despite these diverging explanations for the etiology of this dysconnection, the dysconnection hypothesis consistently predicts impaired functional

integration caused by a breakdown in normal neuronal interactions in SP (Bullmore et al., 1997; Ellison-Wright & Bullmore, 2009; Stephan et al., 2006; Stephan et al., 2009).

Neuroanatomical studies in SP provide the most striking evidence supporting abnormal fronto-temporal connectivity. Abnormalities in the uncinate fasciculus, the most prominent fiber tract containing direct frontal-temporal connections, have been reported in SP. This is seen as reduced fractional anisotropy (FA; Burns et al., 2003; Kawashima et al., 2009; Price et al., 2008; Spoletini et al., 2009; Sussmann et al., 2009; Szeszko et al., 2008; Voineskos et al., 2010), a scalar measure of the degree of directional movement of water molecules detected by diffusion tensor imaging (DTI), as well as in reduced hemisphere anisotropic asymmetry in FA (Kubicki et al., 2002; Park et al., 2004). A link has also been found between this anatomical fronto-temporal disconnect and memory and executive dysfunction in SP. In patients, but not healthy volunteers (HV), lower FA in the uncinate fasciculus has been associated with reduced performance on declarative-episodic verbal memory (Nestor et al., 2004; Nestor et al., 2008), verbal learning memory (Szeszko et al., 2008), and executive functioning (Spoletini et al., 2009). These studies utilized traditional neuropsychological tests that have been associated with particular cognitive abilities and particular brain structures, such as the hippocampus or dorsolateral PFC. However, in order to specifically test the PFC-hippocampal disconnection hypothesis, an appropriate task would be one that required the interaction of the dorsolateral PFC and hippocampus, one that required the integration of working and relational memory.

An example of such a task is the TP task. It has been shown to rely on both working and relational memory, activating both the PFC, including the dorsolateral region, and hippocampus. In the TP task, participants choose between novel stimuli presented in pairs, with the correct choice being a function of the specific pairing: stimulus A is correct when presented with stimulus B; stimulus B is correct when presented with C; stimulus C is correct when presented with A (Figure 1). The relationships between the stimuli in the TP task is similar to the childhood-game “Rock, Paper, Scissors”. The participant must discover, encode, maintain, and then utilize the distinct relationships among the stimuli to perform well at the task. The TP task relies on the hippocampus in both human studies (Moses, Ostreicher, Rosenbaum, & Ryan, 2008; Reed & Squire, 1999; Rickard & Grafman, 1998; Rickard, Verfaellie, & Grafman, 2006) and non-human animal lesion work (Alvarado & Bachevalier, 2005; Alvarado & Rudy, 1995a, 1995b; Alvarado, Wright, & Bachevalier, 2002; Driscoll, Howard, Prusky, Rudy, & Sutherland, 2005). Functional neuroimaging studies, including both functional magnetic resonance imaging (fMRI; Astur & Constable, 2004; Meltzer, Negishi, & Constable, 2008) and magnetoencephalography (MEG; Hanlon et al., 2011; Hanlon et al., 2005; Leirer et al., 2010; Moses et al., 2009), have also demonstrated that TP task performance activates PFC, including the dorsolateral region, in addition to hippocampus. The TP task utilizes the integration of working and relational memory and thus should require the interaction between the dorsolateral PFC and hippocampus.

SP, when contrasted to HV, show abnormal activation of both hippocampus and PFC during TP task performance, as well as a TP task behavioral deficit (requiring more trials to learn and lower percent correct after training) (Hanlon et al., 2011; Hanlon et al., 2005). Using

verbal and nonverbal stimuli versions of the TP task, HV show lateralized hippocampal activation, the left hippocampus activating during the verbal TP task and the right activating during the nonverbal TP task. SP exhibit less lateralized hippocampal activation than HV during the TP task versions (Hanlon et al., 2011; Hanlon et al., 2005). In addition, patients activate the left PFC (Brodmann's Areas 9, 10, 46) during both TP task versions, in contrast to HV activating the right PFC (Brodmann's Areas 9, 10, 46). Thus, HV show both hippocampal and PFC activation during this working-relational memory task, which is impaired in SP.

The hidden-platform version of the VMWT also requires the integration of working and relational memory (dorsolateral PFC-hippocampal network). In this version of the task, the participant must discover, encode, maintain, and then utilize the relationships between spatial cues in this virtual environment to navigate toward a platform hidden under the surface of the water to escape from the pool (allocentric spatial ability; Figure 2). This task has long been known to rely on the hippocampus (MWT in rats: Morris, Garrud, Rawlins, & O'Keefe, 1982; Sutherland, Kolb, & Whishaw, 1982; Sutherland, Whishaw, & Kolb, 1983) (VMWT in humans: Antonova et al., 2009; Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Barkas, Henderson, Hamilton, Redhead, & Gray, 2010; Bartsch et al., 2010; Cornwell, Johnson, Holroyd, Carver, & Grillon, 2008; Goodrich-Hunsaker, Livingstone, Skelton, & Hopkins, 2010), and has also been shown to rely on frontal areas, including the dorsolateral region (MWT in rats: Kolb, Buhrmann, McDonald, & Sutherland, 1994; Kolb, Sutherland, & Whishaw, 1983; Sutherland et al., 1982) (VMWT in humans: Antonova et al., 2009; Folley, Astur, Jagannathan, Calhoun, & Pearlson, 2010). Importantly, SP have hippocampal activation and behavioral (i.e., traveled further and took longer to find the hidden platform) deficits during hidden-platform VMWT performance compared to HV (Folley et al., 2010; Hanlon et al., 2006).

The deficits seen in SP on the TP task and hidden-platform VMWT may at least in part be due to a dysconnection between dorsolateral PFC and hippocampal structures. To further explore this idea, in the present study we interrogated the relationship between fronto-temporal anatomical connectivity and performance on the TP task and VMWT. We proposed that SP would exhibit lower fronto-temporal anatomical connectivity (lower FA in the uncinate fasciculus) compared to HV. We hypothesized that abnormal anatomical connectivity in this PFC-hippocampal network underlies abnormal working and relational memory integration, resulting in lower performance on the TP task and the hidden-platform VMWT. Finally, because everyday functioning in SP is related to memory deficits associated with dorsolateral PFC and hippocampus (Sharma & Antonova, 2003), and should rely on relational and working memory integration, we hypothesized that it would be associated with both fronto-temporal anatomical connectivity and working-relational memory performance. Specifically, lower everyday functioning in patients will be related to lower FA in the uncinate fasciculus and to worse performance on the TP task and the VMWT. Also included were two control tasks, the elemental task and the visible-platform version of the VMWT. The elemental task involves similar pairings of the same type and number of individual stimuli as the TP task (Figure 1), and the visible-platform version of VMWT involves using the keyboard to navigate through the water toward a visible platform, instead of a hidden one. These tasks do not rely on working and relational memory

integration. Thus, they will not show the same patient deficits, nor relationships with FA in the uncinate fasciculus or everyday functioning, seen for the TP task or hidden-platform version of the VMWT, providing specificity to results. The relationships between PFC-hippocampal anatomical connectivity and working-relational memory performance in SP and everyday functioning have not been investigated in SP prior to this study.

Understanding these relationships could potentially lead to the identification of subgroups of SP, differing in degree of PFC-hippocampal connectivity and everyday functioning.

Methods

Participants

Forty-two participants were included in this study: 21 HV and 21 SP (6 females and 15 males in each group). These participants were enrolled as part of a larger project funded by the National Center for Research Resources (5P20RR021938) and the National Institute of General Medical Sciences (8 P20 GM103472) from the National Institutes of Health. Patients were recruited from the outpatient clinics at University of New Mexico (UNM) and the New Mexico VA Medical Health Care System (VAMHCS). HV were recruited from the same geographic location as the SP through community advertisements. Inclusion criteria for patients included diagnosis of schizophrenia, which was determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV SCID-Clinician Version; First, Spitzer, Gibbon, & Williams, 1996). In addition, patients needed to be clinically stable. This was ascertained by the referring clinician with support from relevant psychiatric records that the patient has been clinically stable on the same dose of psychotropic medications for the previous 3 months. HV were excluded if they had any current or past Axis I disorder (assessed with SCID-NP). Inclusion criterion for both HV and SP included: 1) no current or past diagnosis of neurological disorder, history of head trauma (loss of consciousness > 5 min), or mental retardation; 3) no diagnosis of active substance dependence or abuse within the last 12 months (except for nicotine) and no past dependence on or any use in the past 12 months of PCP/Amphetamine/Cocaine; and 5) 18 to 60 years of age. All HV and SP signed informed consent.

All of the HV were right-handed, while two patients were left-handed. All patients with schizophrenia were outpatients who had been stable on either typical (3 on haloperidol and 1 on perphenazine) or atypical (3 on aripiprazole, 2 on olanzapine, 7 on risperidone, 1 on quetiapine, 2 on ziprasidone, and 5 on clozapine) antipsychotic medications for at least 3 months. SP and HV did not differ in sex, age (*HV*: $M=33$, $SD=9.6$; *SP*: $M=38$, $SD=11.6$; $p=.182$), and parental socioeconomic status of primary caregiver (*HV*: $M=5.0$, $SD=1.4$; *SP*: $M=4.4$, $SD=1.9$; $p=.213$). All participants' structural MRIs were read as normal or normal variants by a board-certified neuroradiologist. This research was conducted after review and full approval of the Human Subjects Research Review Committee (HRRC) of the University of New Mexico Health Sciences Center.

Procedures

All procedures (clinical evaluations, task training, and DTI data collection) were performed in a period of approximately eight weeks, during which SP clinical stability and treatment remained unchanged.

Standardized clinical evaluations—Clinical assessments were administered by a trained rater on the same day as task performance. These assessments included the Positive and Negative Symptom Scale (PANSS) and the Clinical Global Impression (CGI) Scale. The UCSD Performance Based Skills Assessment (UPSA-2; Patterson, Goldman, McKibbin, Hughes, & Jeste, 2001) was included to evaluate everyday functioning in patients. The UPSA provides a performance based measure of everyday functioning based on realistic tasks: 1) medication management (understanding of when and amount of medications to take); 2) comprehension/planning (understanding of newspaper article and plan for outing); 3) financial skills (counting money, making change, and paying bills); 4) communication skills (telephone calls); 5) transportation (use of public transportation); and 6) household management (create a shopping list). The UPSA-2 total score ranges from 0 to 120, while the subscale score for each individual category ranges from 0 to 20. Higher scores indicate higher everyday functioning.

TP and elemental tasks—Participants were trained on all four tasks (verbal and nonverbal versions of the TP task and their elemental counterparts). The order of training on the tasks was randomized across participants. For each task, participants were trained to a criterion of 18 correct responses in a row or 200 trials if criterion was not met (Hanlon et al., 2011; Hanlon et al., 2005). Stimuli for the TP task and elemental task nonverbal versions consisted of three different abstract black and white pictures, unique in appearance for each of the tasks (see Figure 1). Stimuli for the TP task and elemental task verbal versions consisted of three pronounceable non-words for each task (see Figure 1). Presentation stimulus software version 13.1 (Neurobehavioral Systems) was used to present stimuli. On each trial, two stimuli were presented simultaneously, one centered on the left side of the screen and one centered on the right (see Figure 1). Within each task, each stimulus was balanced for left and right side presentation in a randomized order, and presentation of the different pairings was randomized. The participant was asked to choose which of the two stimuli was correct via a mouse button press. For the TP task versions, stimuli A, B, and C were used (Figure 1). A is correct when presented with B. B is correct when presented with C. C is correct when presented with A. There are three pairs of stimuli for each version (nonverbal vs. verbal) of the task. For the elemental task, like the TP task, there are three stimuli for the verbal and nonverbal versions of the task. The pairing and presentation of the elemental task was identical to the TP task except that the relationships between correct and incorrect stimuli were different. For the elemental task versions, stimulus D is correct when presented with E. Stimulus E is correct when presented with F. Stimulus D is correct when presented with F. For all of the tasks, each pair of stimuli was presented until the participant responded or until 3 s had passed. The response was followed by a feedback tone, high-pitched if correct and low-pitched if not correct. There was a randomly jittered 3 to 5 s inter-trial interval (ITI) from button press or end of the 3 s window until the next stimulus onset, during which a fixation cross appeared in the middle of the screen. Performance measures

examined included the number of trials to reach criterion (18 correct in a row or 200 maximum trials) and percent correct during 60 trials (collected during magnetoencephalography (MEG: 5 HV and 3 SP) or functional magnetic resonance imaging (fMRI: 16 HV and 16 SP) after the completion of training. The presentation, task order, and instructions for the tasks were the same for training, MEG scan, and fMRI scan, except for the fMRI scan having a longer jittered ITI of 8 to 12 s to facilitate sampling of the hemodynamic response (Burock, Buckner, Woldorff, Rosen, & Dale, 1998). A detailed description of the MEG/fMRI results is beyond the scope of the present discussion. These functional neuroimaging data will be included in a future publication, as the data from each modality includes a slightly different sample of participants (i.e., not all patients were able to complete both scans), examining different hypotheses.

VMWT—Task procedures were those of Hamilton et al. (2003) and Hanlon et al. (2006). Participants were tested on two versions of the task. In both versions, navigation to a goal (platform) was measured with a computerized (virtual) version (NeuroInvestigations, Version 1.2) of the MWT (VMWT; Hamilton et al., 2003; Hamilton & Sutherland, 1999; Hanlon et al., 2006). The participant navigates in a virtual environment consisting of a room with a square floor-plan and a circular pool in the center (Figure 2). All four walls of the room are identical in appearance except for different landmarks flush with the wall to use as spatial cues (four landmarks in total; Figure 2). The field of view is 48 degrees, which allows participants to view one or two cues simultaneously on the display. The surface of the pool consists of an opaque, blue pattern that is tiled via anti-aliasing of the original images to reduce (if not eliminate) any grid-like pattern that could be detected. The pool contains a square platform, 1.75% of the pool area. For analysis the pool's area was divided into four quadrants (Figure 2).

Participants were able to navigate forward, and to turn left and right using the keyboard. The participant's position in the pool was collected in Cartesian coordinates in software every 100 ms. When the platform location was discovered, a bell sounded, and a verbal message saying, "Platform found" appeared on the screen. When the duration of the trial exceeded 60 s without the platform location being found, an aversive tone sounded, the platform became visible, and a verbal message saying, "The platform is visible" appeared on the screen.

In the first version of this task participants learned to navigate to a platform hidden under the surface of the water. The participants were instructed to navigate to the hidden platform as quickly as possible. Each participant received 28 training trials in seven blocks of four trials. The four trials in each block began at different starting locations. The hidden platform was in a fixed position over trials. Starting positions were chosen according to a pseudorandom sequence. If the platform was found within 60 s, the participant remained on the platform for 5 s, during which time they could rotate and view the environment but could not leave the platform. The display was then removed, and a 2 s intertrial interval followed. Latency to find the platform and path length were recorded on these training trials.

After the hidden platform trials, a probe trial was presented in which the platform was removed. Participants, uninformed about platform removal, navigated for 45 s trying to locate the platform. The starting location for the probe trial was selected pseudorandomly

from the two starting locations furthest from the learned platform location (S (bottom) and W (left) starting points in Figure 2). Percentage of the 45 s swim spent in the quadrant that housed the platform during training (northeast or upper right quadrant in Figure 2) was the dependent measure for the probe trial.

The probe trial was followed by a visible platform version of the VMWT. Participants navigated to a visible platform that was in same location that the hidden platform had occupied on previous trials. Participants completed eight trials; two from each of the four starting location in a pseudorandom sequence. Latency (maximum trial length 60 s) and path length to find the platform were recorded.

DTI data collection and analysis—Fronto-temporal anatomical connectivity was assessed using DTI measures of FA in the uncinate fasciculus. DTI data was collected along the AC/PC line, throughout the whole brain, with FOV = 256×256 mm, 128×128 matrix, 72 slices with a slice thickness of 2 mm (isotropic 2 mm resolution), NEX = 1, TE = 84 ms and TR = 9000 ms. A multiple-channel radiofrequency (RF) coil was used, with GRAPPA (X2), 30 gradient directions with $b = 800$ s/mm². The $b = 0$ experiment was repeated five times (Jones, Horsfield, & Simmons, 1999), and equally inter-spread between the 30 gradient directions. The total imaging time was approximately 6 min. This experiment was repeated twice to increase the signal to noise ratio (SNR). The data from the two DTI experiments, each with a dimension of $128 \times 128 \times 72 \times 35$ was concatenated together to form one larger data set of dimension $128 \times 128 \times 72 \times 70$. All $b = 0$ images were registered to the first $b = 0$ image with a 6 degrees-of-freedom transformation. This was followed by registering the $b = 800$ s/mm² image to the $b = 0$ image immediately before it by an affine 12 degrees-of-freedom transformation. The two transformations were multiplied and then one transformation applied to the $b = 800$ s/mm² image to align it to the first $b = 0$ image. This resulted in all images being registered to the first $b = 0$ image. Flirt/FSL was used for all registration steps.

Analysis consisted of the following steps: 1) quality check, any gradient directions with excessive motion or vibration artifacts were identified and removed; 2) motion and eddy current correction; 3) the gradient directions were corrected for any image rotation done during the previous motion correction step; 4) calculation of diffusion tensor and scalar measures such as FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD); 5) spatial normalization by FNIRT/FSL to MNI space; and 6) apply tract based spatial statistics (TBSS/FSL) method to calculate participant specific skeletons (Smith et al., 2006). The TBSS method does not find tracts from one region to another based on eigenvector properties, and is not a tractography method. It is a robust method of doing voxel based comparisons by restricting the analysis to white matter skeletons (Smith et al., 2006). In this analysis, the skeleton was further restricted to uncinate fasciculus as defined by the JHU atlas (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004; see top row of Figure 3 for the uncinate fasciculus skeleton). Group differences were evaluated by comparing group mean values for FA, MD, AD, and RD over the uncinate fasciculus skeleton.

In order to confirm the results found by calculating the mean FA over the uncinate fasciculus skeleton, voxel-by-voxel differences over the same region were examined. A non-

parametric randomise/FSL test (number of permutations = 5000) was performed for the uncinate fasciculus skeleton mask, with multiple comparisons accounted by the threshold-free cluster approach (TFCE; (Smith & Nichols, 2009)).

Regression analyses—Hierarchical linear regressions were conducted to evaluate the contribution of fronto-temporal anatomical connectivity (FA in the uncinate fasciculus) to behavioral performance on working-relational memory tasks (TP task and VMWT) and control tasks (elemental task) and how diagnostic group affects these relationships. A strong correlation between right- and left-hemisphere uncinate fasciculus FA ($r = .905, p < .001$) suggests that their shared variance would result in similar relationships with behavioral measures. Thus, to reduce the amount of regressions performed, a factor score based on bilateral FA values was created using principal component analysis. This FA factor score was then used in the hierarchical regression analyses. Task performance was the dependent variable (DVs; Regression 1: nonverbal TP task, number of trials to criterion; Regression 2: verbal TP task, trials to criterion; Regression 3: nonverbal elemental task, trials to criterion; Regression 4: verbal elemental task, trials to criterion; Regression 5: VMWT, percent time spent in the correct quadrant during the probe trial). Each hierarchical regression included the following independent variables (IVs) placed in the linear model in the following order: (1) Group; (2) FA in the uncinate fasciculus (bilateral factor score); and (3) their interaction (Group x FA). These analyses determined the variance (R^2) of the DV accounted for by Group, as well as the incremental variance or change in R^2 (ΔR^2) contributed by FA in the uncinate fasciculus, and their interaction term.

Three linear regressions were done to evaluate the relationship between everyday functioning (DV: UPSA-2 total score) in SP and FA in the uncinate fasciculus (FA factor score) (1), performance on working-relational memory tasks (2), and performance on control tasks (3). The relationship between positive and negative symptoms with FA in the uncinate fasciculus in SP is not clear as some report a relationship with positive symptoms (Cheung et al., 2011; Skelly et al., 2008), others with negative symptoms (Szeszko et al., 2008), and others not finding a relationship (McIntosh et al., 2008; Price et al., 2008). Therefore, the same three linear regressions performed with everyday functioning were conducted with positive (DV: PANSS Positive Symptoms Score) and negative (DV: PANSS Negative Symptoms Score) symptoms.

Results

Clinical Findings

Recruited patients were mildly to moderately ill, with a mean CGI severity score of 3.52 ($SD = .75$) and a PANSS Positive Symptoms mean score of 15 ($SD = 5$), Negative Symptoms of 14 ($SD = 4$), General of 24 ($SD = 8$), and Total of 52 ($SD = 12$). The UPSA-2 mean subscale scores for each category based on 20 patients (one patient's data was not collected) are as follows: 1) medication management: $M = 16, SD = 5$; 2) comprehension / planning: $M = 13, SD = 3$; 3) financial: $M = 18, SD = 2$; 4) communication: $M = 16, SD = 2$; 5) transportation: $M = 15, SD = 3$; 6) household: $M = 16, SD = 3$; and 7) total score: $M = 94, SD = 13$.

Behavioral Findings

Two patients (1 female and 1 male) withdrew from the study after training on the TP and elemental tasks. Thus, their data is missing for the entire VMWT, and the TP and elemental tasks after training. Fortunately, their training and DTI data could still be analyzed. Also, one patient's data was not collected for the nonverbal elemental task, during and after training, due to exceeding the time allocated for training.

TP and elemental tasks—As predicted, SP performed worse (required more trials to learn and had lower percent correct after training) on both versions of the TP task, verbal and nonverbal, than did HV. A repeated-measures analysis of variance (ANOVA) using Version (verbal and nonverbal) and Task (TP and elemental) as within-participant variables and Group (SP and HV) as the between-participants factor was performed for each of the behavioral measures (number of trials to meet criterion and percent correct after training). Examining the number of trials to reach criterion, there were significant effects for Group, $F(1,39) = 21.66, p < .001$ and Task, $F(1,39) = 60.36, p < .001$, with a trend toward a Group $\times$ Task interaction, $F(1,39) = 3.50, p = .069$ (see Figure 4). Thus, patients required more trials during training than HV for both versions of the TP and elemental tasks (no Version, Version $\times$ Group, Version $\times$ Task, or Version $\times$ Task $\times$ Group effects) and this tended to be worse for the TP task versions than the elemental task versions. Importantly, this trend was significant when examining percent correct for the first 60 trials after training. Groups differed on performance, depending on the task and the version (Group: $F(1,37) = 9.81, p = .003$; Task: $F(1,37) = 55.79, p < .001$; Task $\times$ Group: $F(1,37) = 14.35, p = .001$; Task $\times$ Group $\times$ Version: $F(1,37) = 4.68, p = .037$). Exploring these significant effects further, it was found that patients performed worse (lower percent correct) than HV on both the verbal TP task ($F(1,39) = 17.74, p < .001$) and nonverbal TP task versions ($F(1,39) = 7.36, p = .010$), but did not show a performance decrement on the verbal or nonverbal elemental tasks (see Figure 4). Therefore, as predicted, SP required more trials to learn the verbal and nonverbal versions of the TP task and performed worse on them after training than HV.

VMWT hidden-platform version—Over the 28 trials of training, SP ($M = 47\%$, $SD = 15$) spent less time in the correct quadrant than did HV ($M = 60\%$, $SD = 8$; $F(1,39) = 12.45, p = .001$). Patients took longer than HV to locate the hidden platform (Group: $F(1,38) = 11.57, p = .002$). Latency decreased linearly with practice for participants generally (linear Block: $F(1,38) = 50.84, p < .001$), but not differentially by group (Group $\times$ linear Block interaction). Importantly, patients were slower to reach the platform overall than HV, and were also slower after sufficient practice locating the platform (Block 7: $F(1,39) = 9.42, p = .004$).

Figure 5 shows total path length as a function of group and block. Similar to escape latency, there was an overall group difference in path length to locate the hidden platform (Group: $F(1,38) = 7.00, p = .012$), with patients having greater path length. Path length decreased with practice for participants generally (linear Block: $F(1,38) = 13.96, p = .001$), but not differentially by group (Group $\times$ linear Block). Patients took a longer path than did HV to locate the hidden platform overall and in the last block of trials (Block 7: $F(1,39) = 8.70, p$

= .005). In summary, patients were slower and took a longer path than HV during the VMWT hidden-platform version.

VMWT probe trial—Figure 5 (lower panel) shows that patients spent less time in the correct quadrant of the pool during the probe trial than did HV, $F(1,39) = 16.92, p < .000$. Importantly, there was no difference between patients and HV in mean path length during the probe trial, $F(1,39) = 1.35, p = .252$, verifying that both groups were searching for the platform and that patients were engaged in the task.

VMWT visible-platform version—Escape latency and path length to locate the visible platform did not significantly decrease with practice for participants generally (linear Block), nor differentially by group (Group $\times$ linear Block). Importantly, patients did not take significantly more time or path length to locate the visible platform. In addition, there was no Group difference in percent time spent in the correct quadrant (HV: $M = 57\%$, $SD = 3$; SP: $M = 56\%$, $SD = 5$). Therefore, patients did not show detectable behavioral impairments on the visible-platform variant of the VMWT.

DTI Findings

Since age-related deficits have been reported for uncinate fasciculus FA in SP (Rosenberger et al., 2008), age was used as a covariate in the DTI analyses. When examining FA and MD in the uncinate fasciculus, significant Hemisphere and Group main effects were found for FA (Figure 6), but not MD. Overall, FA in the uncinate fasciculus was found to be lower in the right hemisphere than the left ($F(1,39) = 5.96, p = .019$) and lower in SP compared to HV ($F(1,39) = 9.62, p = .004$). There were no interactions between Group, Age, and Hemisphere for either FA or MD. Figure 6 shows the distribution of FA values for all participants and the strong correlation that was found between right- and left-hemisphere uncinate fasciculus FA ($r = .905, p < .001$). To follow up on the FA group difference, AD and RD were examined. There were no significant effects found.

In order to confirm the above results, voxel-by-voxel differences over the same region were examined. A non-parametric randomise/FSL test was performed for the uncinate fasciculus skeleton mask. The regions with significant group differences are shown (in red voxels) in the bottom row of Figure 3 at p -value = 0.05, with multiple comparisons accounted by the TFCE approach (Smith & Nichols, 2009). Again, SP showed lower FA in bilateral uncinate fasciculus.

Regression Analyses

The top of Table 1 illustrates the results of hierarchical linear regressions examining the TP task versions and FA in the uncinate fasciculus (bilateral factor score). These analyses were done to determine how much fronto-temporal anatomical connectivity contributes to performance on the TP task versions and whether groups differ in this relationship. Results showed that Group accounts for a significant amount of the performance variance for both versions of the TP task (15% for nonverbal TP and 28% for verbal TP; see Table 1). Focusing on the change in R^2 for FA in the uncinate fasciculus, results show that it accounts for a significant amount of the variance in performance on verbal and nonverbal TP task

versions. FA accounts for 10% of the variance for the nonverbal TP task and 19% of the variance for the verbal TP task, above the variance accounted for by Group. This is the case for both SP and HV, since the change in R^2 for the interaction term was not significant for either of the TP task regressions. The β shows a negative relationship: regardless of Group, a higher number of trials to learn the TP task (lower performance) is related to lower FA in the uncinate fasciculus (lower fronto-temporal anatomical connectivity).

Table 1 also illustrates these same analyses for the elemental task versions. In strong contrast to the above TP task results, FA in the uncinate fasciculus did not account for a significant amount of the elemental task performance variance. The Group $\times$ FA interaction terms also did not reach significance for either elemental task version. The only significant effects were of Group for the verbal elemental task. Patients required more trials to learn the verbal elemental task than HV, and performance on both versions of the elemental task was not related to fronto-temporal anatomical connectivity.

At the bottom of Table 1, regression results are displayed for the VMWT using performance on the probe trial (percent of time spent in the correct quadrant) as the DV. Results were similar to that seen for the TP task. Results showed that Group accounts for a significant amount of the performance variance during the probe trial (31%). Focusing on the change in R^2 , FA in the uncinate fasciculus accounts for a significant amount of the variance in probe trial performance (14%), above the variance accounted for by Group. Since the change in R^2 for the interaction term was not significant, this is the case for both SP and HV. The β shows a positive relationship, so regardless of Group, the less time spent in the correct quadrant during the probe trial (lower performance), the less FA in the uncinate fasciculus (lower fronto-temporal anatomical connectivity).

The top of Table 2 shows the results for the linear regression analyses examining everyday functioning (measured with the UPSA-2) in patients and 1) FA in the uncinate fasciculus; 2) working-relational memory performance measures (nonverbal and verbal TP task versions' trials to reach criterion and mean path length over trials to locate the hidden platform for the VMWT); and 3) control measures (nonverbal and verbal elemental task versions' trials to reach criterion and mean path length over trials to locate the visible platform for the VMWT). For the first linear regression, FA in the uncinate fasciculus accounts for a significant amount of variance (24%) in UPSA-2 total score. The β is positive for this relationship, indicating that the lower the UPSA score (lower everyday functioning), the less FA in the uncinate fasciculus (lower fronto-temporal anatomical connectivity). For the second regression, three measures of working-relational memory performance from the TP task and VMWT were in the model together. Overall, these measures accounted for 53% of the variance of the UPSA score ($p = .012$). Due to the significance of this result, a follow-up analysis was done in which each of the three working-relational memory performance measures were regressed separately on UPSA score. Each of the three measures accounted for a significant amount of the UPSA variance. In addition, all three had negative β s, indicating that lower everyday functioning was related to lower working-relational memory performance (lower PFC-hippocampal memory integration). In contrast, this relationship was not significant for the control task measures. When all three control measures were added into the regression model together, they only accounted for 4% of the UPSA score

variance, as opposed to the 53% seen with the working-relational memory performance measures. Thus, overall both fronto-temporal anatomical (uncinate fasciculus FA) and performance (TP task and VMWT) measures accounted for a significant amount of the variance in everyday functioning (UPSA score). In patients, lower fronto-temporal white-matter connectivity was related to lower everyday functioning.

The bottom of Table 2 shows the results for the linear regression analyses examining negative and positive symptoms (measured with the PANSS) in patients and 1) FA in the uncinate fasciculus; 2) working-relational memory performance measures; and 3) control measures. There were no significant relationships found.

Discussion

This study directly tested the dysconnection hypothesis in SP by examining fronto-temporal anatomical connectivity (FA in the uncinate fasciculus) and dorsolateral PFC-hippocampal memory integration (working-relational memory performance) and their relationship with each other and everyday functioning in schizophrenia. SP showed a performance deficit on two working-relational memory tasks relative to HV. SP required more trials to learn the TP task than did HV and exhibited a lower level of performance after training, with no decrement after training on an elemental control task. These performance results replicate those found in Hanlon et al. (2011; 2005). Consistent with Hanlon et al. (2006), SP required more time and traveled farther to find a hidden platform on the VMWT than did HV. Further, patients searched less time in the correct quadrant during a probe trial. These results support the notion of a dorsolateral PFC-hippocampal memory integration deficit in SP.

SP were found to have lower fronto-temporal anatomical connectivity, as indexed by lower FA in the right and left uncinate fasciculus compared to HV. This replicates previous research (Kawashima et al., 2009; Szeszko et al., 2008). As a measure of the degree of directionally coherent movement of water molecules, reduced FA in the uncinate fasciculus of SP implies a reduction in white matter integrity. Also, right-hemisphere FA was lower than left for both groups. Kubicki et al. (2002) found this same pattern in HV, but not in SP. However, Kubicki et al. (2002) also found only the left-hemisphere FA to be decreased, in contrast to the present results of a bilateral decrease. This difference between studies is seen by others as well, with some finding a lateralized left-hemisphere decrease in uncinate fasciculus FA (Burns et al., 2003; Kubicki et al., 2002; Voineskos et al., 2010) and others finding a bilateral reduction (Kawashima et al., 2009; Szeszko et al., 2008). MD is a measurement of total water displacement in each direction, averaged for the three directions in space. SP did not show a difference from HV for MD in the uncinate fasciculus, as was reported by Kawashima et al. (2009).

A unique and important finding in this study was the relationship found between fronto-temporal anatomical connectivity and working-relational memory performance. We found that FA in the uncinate fasciculus shared a significant amount of variance with performance measures from both the TP task and VMWT, beyond that shared with group. Thus, regardless if a participant was a HV or a SP, lower fronto-temporal anatomical connectivity (less FA) was related to lower working-relational memory performance as measured by

performance on the TP task and VMWT (Table 1). In addition, lower fronto-temporal anatomical connectivity and lower working-relational memory performance predicted worse everyday functioning in SP (Table 2).

Both the TP task and the hidden-platform version of VMWT utilize relational memory, forming and relying on the relations between unique combinations of stimuli, and working memory, maintaining and using these relationships for a short time period. To employ newly formed relationships between stimuli in working memory, the dorsolateral PFC must access these relational representations, most likely from the structure that formed them, the hippocampus. Thus, the integration and use of novel relationships between distinct elements in working memory should involve interactions between the dorsolateral PFC and hippocampus. In support of this notion, the acquisition of the TP task and VMWT relationships activate both PFC, including dorsolateral regions, and hippocampus (TP task: Astur & Constable, 2004; Hanlon et al., 2011; Hanlon et al., 2005; Leirer et al., 2010; Meltzer et al., 2008; Moses et al., 2009) (VMWT: Antonova et al., 2009; Folley et al., 2010), and there is some preliminary evidence for PFC and hippocampal interaction during TP task performance (Meltzer, Fonzo, & Constable, 2009). In addition, lateral PFC may be increasingly involved in relational tasks, such as the TP task, once the relationships are well formed and must be maintained (Doeller, Opitz, Krick, Mecklinger, & Reith, 2005). The current findings of correlations between behavioral deficits on tasks that rely on working-relational memory integration and a measure of fronto-temporal anatomical connectivity lend support to the idea of abnormal interaction between dorsolateral PFC and hippocampus in schizophrenia. Therefore, this data support the fronto-temporal dysconnection (anatomical and functional) hypothesis in schizophrenia.

Importantly, SP did not show a behavioral decrement on either control task, the visible-platform version of the VMWT and the elemental task. For the elemental task versions, SP did require more trials to learn. However, they were able to learn the task, performing both versions above 90% accuracy after training. This task involves similar pairings of the same type and number of individual stimuli as the TP task, however, the pairings do not require discovery and use of relations between the individual stimuli. Similarly, the visible-platform version of VMWT does not require relational memory, as the participant does not have to use the relationship between stimuli on the walls to locate the platform, but only needs the ability to use the keyboard to navigate through the water toward a visual goal to escape the pool. Thus, the elemental task and the visible-platform VMWT are particularly valuable control tasks for studying the interaction between dorsolateral PFC and hippocampus, as both may require some working memory, although neither requires relational memory. The interaction between dorsolateral PFC and hippocampus is not needed for successful performance on either control task. Therefore, it is not surprising that fronto-temporal anatomical connectivity (FA in the uncinate fasciculus) was not associated with performance on either version of the elemental task, as it was with the TP task. In addition, using the same performance measure from the elemental (trials to reach criterion on both nonverbal and verbal versions) and visible-platform version of VMWT (path length) as were used for the TP task and the hidden-platform version, there was no association found with everyday functioning (Table 2). Overall, in contrast to findings with the PFC-hippocampal dependent

tasks, SP did not show a behavioral deficit on the control tasks once learned, nor were these tasks associated with anatomical connectivity or everyday functioning.

A novel and exciting finding in this study is that both working-relational memory performance and anatomical connectivity were associated with everyday functioning in SP. Even in light of adequate control of psychiatric symptoms, SP still display poor everyday functioning, seen socially (Nanko & Moridaira, 1993), occupationally (Lehman et al., 2002), and in the ability to live independently (Scott, 1993). Everyday functioning in SP has been found to be related to memory deficits, most consistently with declarative, episodic, and working memory (Sharma & Antonova, 2003). We believe that memory dysfunction, particularly the integration of working and relational memory as elucidated with the TP task and the VMWT, is a key component of this reduced functioning capacity in SP. Being able to function socially and occupationally, and to live independently, all require the ability to learn new and remember old relationships (relational memory), and use this information in an effective manner (working memory). Therefore, productive daily functioning requires the integration of working and relational memory (i.e., normal dorsolateral PFC and hippocampal connectivity). Our results support this idea, finding that working-relational memory performance (dorsolateral PFC-hippocampal memory integration) accounts for a significant amount of variance in everyday functioning (UPSA). Fronto-temporal anatomical connectivity may underlie this relationship, since FA in the uncinate fasciculus accounted for a significant amount of variance for both working-relational memory performance and everyday functioning. It should be noted, that this relationship does not preclude other brain networks underlying everyday functioning in SP as well.

Future studies examining the specificity of the present findings should test the extent to which the relationships found with the TP task and VMWT, which rely on the integration of working and relational memory, are also seen with tasks that rely only on relational memory or only on working memory, and if so, how these relationships compare. Another test of the specificity of the present findings would be the inclusion of another network, task and white matter tract that has been found to be abnormal in schizophrenia and may also be related to everyday functioning. Future work should also include a larger sample size. To keep the ratio of predictors to sample size lower we have restricted the number of regressions performed by creating a factor score based on bilateral uncinate fasciculus FA values. A larger sample size would allow for FA hemisphere comparisons. Finally, we would like to note that a decrease in FA does not have a specific cause and can be caused by multiple factors, including axonal degradation or demyelination. Magnetization transfer ratio is another complimentary parameter that is sensitive to myelination and can help in future work to understand the mechanism of FA changes in SP (Kubicki et al., 2005). In conclusion, our results support a fronto-temporal dysconnection (anatomical and functional) in schizophrenia, which is associated with lower everyday functioning. Understanding these relationships could potentially lead to the identification of subgroups of SP, differing in degree of PFC-hippocampal connectivity and everyday functioning. Knowing where the patient lies on a continuum of functioning and network connectivity may help identify specific treatment strategies, such as cognitive remediation, that would be most successful.

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Nonverbal TP

Verbal TP

Nonverbal Elemental

Verbal Elemental

Figure 1.

Upper panel: On each trial, two stimuli were presented simultaneously, one centered on the left side of the screen and one centered on the right. This illustrates the six possible stimulus arrangements that are presented randomly and one at a time to the participant for the nonverbal TP task. The participant was asked to choose which of the two stimuli was correct via a mouse button press. In this figure, an asterisk was placed under the correct stimulus for each pair. Lower panel: Stimuli and their relationship to one another for the nonverbal and verbal versions of the TP and elemental tasks. For the TP nonverbal and verbal task

versions, stimulus A is correct when presented with stimulus B. Stimulus B is correct when presented with C. Stimulus C is correct when presented with A. For the Elemental nonverbal and verbal task versions, stimulus D is correct when presented with E. Stimulus E is correct when presented with F. Stimulus D is correct when presented with F. The gray arrows indicate the difference between the stimuli relations used in the TP task versions versus those used in the elemental task versions.

Figure 2.

VMWT environment. Upper panel: Participant's view while searching for the hidden platform. One of the four distal cues, the pool surface, and two pool walls are shown. Lower panel: An aerial view of the virtual environment, with the four vertical walls flattened. The circular pool is positioned in the center of the room. The hidden platform is shown as a black square within the northeast (upper right) quadrant of the pool. There are four walls with a cue placed on each.

Figure 3.

The top row shows the TBSS analysis. It illustrates the uncinate fasciculus skeleton mask (in green color) in three slices (MNI z coordinate indicated) shown over the mean FA image for all participants. Group differences were examined using the mean FA calculated over this uncinate fasciculus skeleton. The bottom row shows the nonparametric randomise/FSL test, run with 5,000 permutations. The voxels (in red color) denote significant group differences ($p = .05$), SP exhibiting lower FA bilaterally. Multiple comparisons were accounted for with the TFCE approach. Radiological convention is used.

Figure 4.

SP and HV performance on the TP and elemental task versions for (upper panel) number of trials to reach criterion (18 consecutive trials in a row correct or 200 trials) and (lower panel) mean percent correct for the first 60 trials after training. Error bars indicate SE. Patients took more trials to reach criterion (upper panel) and performed worse after training (lower panel) compared to HV for the verbal and nonverbal TP task. For the control elemental (EL) task versions, patients required more trials to learn the task (upper panel). Importantly, once the

EL task versions were learned, there was no group difference seen for performance (lower panel).

Figure 5.

Upper panel: Patients traveled farther over the seven blocks of trials (four trials per block) to locate the VMWT hidden platform than HV. Importantly, there was no group difference in path length traveled to locate the visible platform (two blocks of four trials). Path length is expressed as the ratio of the total path length to the diameter of the pool. Bars indicate SE. Note: SE bars are not apparent around means for the visible version of the task because the values were very small. Lower panel: The pseudocolor circles show average composite dwell time for each group during the probe trial. Prior to platform removal for the probe

trial, it was located in the northeast (upper right) quadrant. Areas in yellow depict regions occupied for a relatively high percentage of the time, whereas areas in red were occupied a relatively low percentage of the time. HV spent more time in the correct quadrant than SP.

Figure 6.

Upper panel: SP showed lower FA in the uncinate fasciculus compared to HV in the left and right hemispheres. Overall, FA in the uncinate fasciculus was found to be lower in the right hemisphere than the left. Lower panel: This scatter plot illustrates the distribution of FA values for all participants and the strong correlation that was found between right and left-hemisphere uncinate fasciculus FA ($r = .905$, $p < .001$).

Table 1

Hierarchical Linear Regression analyses with Performance on Nonverbal and Verbal TP, Elemental, and hidden-platform VMWT as the Dependent Variables and Group, FA in Uncinate Fasciculus (bilateral FA factor score), and their Interaction as the Independent Variables.

		R²	F	p	β
DV	1. Nonverbal TP - Trials to Criterion				
IVs	Group	0.153	7.24	0.010	0.391
	<i>R</i> Change for FA (bilateral factor score)	0.104	5.46	0.025	-0.368
	<i>R</i> Change for Interaction of Group and FA	0.001	0.05	0.824	0.032
DV	2. Verbal TP – Trials to Criterion				
IVs	Group	0.278	15.38	0.000	0.527
	<i>R</i> ² Change for FA (bilateral factor score)	0.192	14.08	0.001	-0.500
	<i>R</i> ² Change for Interaction of Group and FA	0.019	1.39	0.247	-0.141
DV	3. Nonverbal EL Trials to Criterion				
IVs	Group	0.088	3.75	0.060	0.296
	<i>R</i> ² Change for FA (bilateral factor score)	0.001	0.06	0.807	-0.043
	<i>R</i> ² Change for Interaction of Group and FA	0.009	0.37	0.545	-0.099
DV	4. Verbal EL – Trials to Criterion				
IVs	Group	0.264	14.35	0.001	0.514
	<i>R</i> ² Change for FA (bilateral factor score)	0.000	0.00	0.972	0.006
	<i>R</i> ² Change for Interaction of Group and FA	0.000	0.01	0.919	-0.015
DV	5. Probe Trial – % Time in Correct Quadrant				
IVs	Group	0.308	16.92	0.000	-0.555
	<i>R</i> ² Change for FA (bilateral factor score)	0.142	9.57	0.004	0.428
	<i>R</i> ² Change for Interaction of Group and FA	0.030	2.09	0.157	0.179

Table 2

Linear Regression Analyses in SP with UPSA Total Score, PANSS Negative Symptoms Score, and PANSS Positive Symptoms Score as the Dependent Variables and FA in Uncinate Fasciculus (bilateral FA factor score) and Performance Measures on Working-Relational Memory Tasks and Control Tasks as Independent Variables.

		R²	F	p	β
DV	1. UPSA Total Score				
IV	FA (bilateral factor score)	0.242	5.75	0.028	0.492
DV	2. UPSA Total Score				
IVs	Working-Relational Memory Measures Together	0.533	5.32	0.012	
	#1: Nonverbal TP – Trials to Reach Criterion	0.234	5.50	0.031	–0.484
	#2: Verbal TP – Trials to Reach Criterion	0.265	6.48	0.020	–0.514
	#3: VMWT Hidden Platform – Path Length	0.420	11.58	0.004	–0.648
DV	3. UPSA Total Score				
IVs	Control Measures Together	0.039	0.17	0.912	
	#1: Nonverbal EL – Trials to Reach Criterion				
	#2: Verbal EL – Trials to Reach Criterion				
	#3: VMWT Visible Platform – Path Length				
DV	1. PANSS Negative Symptoms Score				
IV	FA (bilateral factor score)	0.062	1.27	0.275	
DV	2. PANSS Negative Symptoms Score				
IVs	Working-Relational Memory Measures Together	0.251	1.68	0.215	
DV	3. PANSS Negative Symptoms Score				
IVs	Control Measures Together	0.185	1.06	0.398	
DV	1. PANSS Positive Symptoms Score				
IV	FA (bilateral factor score)	0.133	2.91	0.104	
DV	2. PANSS Positive Symptoms Score				
IVs	Working-Relational Memory Measures Together	0.188	1.16	0.359	
DV	3. PANSS Positive Symptoms Score				
IVs	Control Measures Together	0.171	0.96	0.437	