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Bilateral Hippocampal Dysfunction in Schizophrenia

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Abstract

The hippocampus has long been known to be important for memory, with the right hippocampus particularly implicated in nonverbal/visuo-spatial memory and left in verbal/narrative or episodic memory. Despite this hypothesized lateralized functional difference, there has not been a single task that has been shown to activate both the right and left hippocampus differentially, dissociating the two, using neuroimaging. The transverse patterning (TP) task is a strong candidate for this purpose, as it has been shown in human and nonhuman animal studies to theoretically and empirically depend on the hippocampus. In TP, participants choose between stimuli presented in pairs, with the correct choice being a function of the specific pairing. In this project, TP was used to assess lateralized hippocampal function by varying its dependence on verbal material, with the goal of dissociating the two hippocampi. Magnetoencephalographic (MEG) data were collected while controls performed verbal and nonverbal versions of TP in order to verify and validate

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lateralized activation within the hippocampi. Schizophrenia patients were evaluated to determine whether they exhibited a lateralized hippocampal deficit. As hypothesized, patients' mean level of behavioral performance was poorer than controls' on both verbal and nonverbal TP. In contrast, patients had no decrement in performance on a verbal and nonverbal non-hippocampal-dependent matched control task. Also, controls but not patients showed more right hippocampal activation during nonverbal TP and more left hippocampal activation during verbal TP. These data demonstrate the capacity to assess lateralized hippocampal function and suggest a bilateral hippocampal behavioral and activation deficit in schizophrenia.

Keywords

schizophrenia; hippocampus; lateralized; magnetoencephalography (MEG); transverse patterning; memory

(1) Introduction

The development of a non-invasive assessment technique that can be used to dissociate right and left hippocampal function is critical for understanding the neural and cognitive deficits associated with schizophrenia. The hippocampus plays a central role in visual and verbal memory impairments exhibited in schizophrenia (Cirillo and Seidman, 2003; Saykin et al., 1991, 1994; Tamminga et al., 2010). Further, some suggest that hippocampal deficits are more pronounced in the left hemisphere than in the right in schizophrenia (Harrison, 2004; Shenton et al., 2001). The identification of hippocampal lateralization abnormalities may lead to a better understanding of the neurodevelopmental processes in schizophrenia. For example, observation of reduced hippocampal functional lateralization in schizophrenia would support and enrich theoretical models of schizophrenia in which neurodevelopmental abnormalities lead to atypical lateralization (Crow, 1997; Petty, 1999; Sommer et al., 2001; Yeo et al., 1999). Unfortunately, little conceptual or empirical work is available that directly addresses lateralized hippocampal function in psychopathology.

One challenge in studying hippocampal functional lateralization is the development of tasks that have appropriate psychometric properties and are suitable for neuroimaging contexts. The choice of task should be motivated by a theory of hippocampal function. Hippocampus has long been understood to be important for memory function, with right hippocampus contributing to visuo-spatial memory (Burgess et al., 2002; Smith and Milner, 1981, 1989) and left hippocampus to verbal/narrative or episodic memory (Burgess et al., 2002; Frisk and Milner, 1990). However, this lateralization of hippocampal function is not always observed (Astur et al., 2002; Maguire et al., 1996a; Ryan et al., 2001; Viskontas et al., 2000). Both visuo-spatial and episodic memory are thought to require the capacity to relate or combine stimuli to form unique representations of the conjunction of those stimuli (relational mnemonic abilities), in which the hippocampus is theorized to play a central role (Cohen and Eichenbaum, 1993; Rudy and Sutherland, 1995). We suggest that it is the absence or presence of reliance on verbal processing in a relational task that distinguishes right and left hippocampal functioning. Thus, visuo-spatial memory, primarily a nonverbal relational task, should engage right hippocampus, and verbal/narrative or episodic memory,

primarily a verbal relational task, should involve left hippocampus. Therefore, to assess lateralized hippocampal dysfunction, a task is needed that is known to rely specifically on relational mnemonic abilities, in which verbal reliance can be manipulated. Such a task would be a more direct test of hippocampal function than traditional neuropsychological tests of visuo-spatial and episodic memory, which may involve other cognitive abilities.

Recent studies have attempted to use relational mnemonic tasks, which are specific to hippocampus, to assess hippocampal function in schizophrenia (Coleman et al., 2010; Öngür et al., 2006; Hanlon et al., 2005, 2006; Titone et al., 2004). One of these tasks is the transverse patterning (TP) problem, which involves a completely overlapping set of relationships among stimuli. In TP, participants choose between stimuli presented in pairs, with the correct choice being a function of the specific pairing: A is correct when paired with B, B is correct when paired with C, and C is correct when paired with A. The participant does not know which stimulus is correct, unless they know what it is paired with. To perform this choice-reaction-time task, the participant must discover and encode the distinct relationships among the stimuli. Hippocampal damage impairs TP performance in mice (Rondi-Reig et al., 2001), rats (Alvarado and Rudy, 1995a, 1995b; Driscoll et al., 2005), non-human primates (Alvarado and Bachevalier, 2005; Alvarado et al., 2002), and humans (Moses et al., 2008; Reed and Squire, 1999; Rickard and Grafman, 1998; Rickard et al., 2006). Based on such studies, it is clear that TP depends on hippocampal function. In contrast, in a non-hippocampal elemental task, which involves similar pairings of the same type of individual stimuli, the pairings do not require discovery and use of relations between the individual stimuli as TP does. With proper psychometric evaluation and adjustment, in light of classic but challenging issues of task matching and differential deficit (Chapman and Chapman, 1973, 2001), the elemental task can be used to confirm the hippocampal dependence and specificity of TP (see Hanlon et al., 2005, for TP and elemental task matching).

Using a hard to verbalize, “nonverbal”, version of TP and two hard to verbalize, “nonverbal”, non-hippocampal dependent tasks, including the elemental task, Hanlon et al. (2005) found a behavioral deficit specific to TP performance in schizophrenia patients. In addition, using magnetoencephalography (MEG), a neuroimaging technique that characterizes neuronal population activity through the detection of the magnetic field generated by current flow in the brain, Hanlon et al. (2005) showed right hippocampal activation in controls during this nonverbal TP version and more bilateral or left hippocampal activation in schizophrenia patients. These findings strongly suggest a right hippocampal deficit in schizophrenia. However, they do not rule out an additional left hippocampal deficit. Remarkably, patients have not been systematically tested on a relational task that can assess the independent function of both the right and left hippocampus.

The present study was a replication and extension of Hanlon et al. (2005), which used only nonverbal TP and control tasks. Verbal versions of the TP and elemental tasks were developed and included in the training and MEG sessions. Thus, MEG and behavioral data assessed right and left hippocampal function in new samples of schizophrenia patients and controls. It was hypothesized that MEG would confirm the lateralized activation of the

hippocampus (nonverbal TP activating the right, verbal TP activating the left) in controls. Schizophrenia patients were expected to show a hippocampal-dependent behavioral impairment that was not lateralized, found on both TP versions. In contrast, schizophrenia patients' performance was expected to be similar to control participants' on a nonverbal and verbal version of the elemental control task, which is not hippocampal-dependent. This similarity in performance (as seen in Hanlon et al., 2005) is valuable for ruling out a generalized deficit as a confound in interpreting results. Patients were also predicted to show bilateral hippocampal activation for both TP versions using MEG, and thus, lacking the lateralized hippocampal activation found in control participants.

Activation within the prefrontal cortex (PFC) during TP was possible. The TP task requires not only relational memory but also working memory for maintaining the distinct relationships, and thus the PFC (Baddeley, 1986, 2003; Goldman-Rakic, 1994). In addition, recent research using the TP task during both MEG and fMRI has found activation of the PFC in control participants (Meltzer et al., 2008; Moses et al., 2009). Accordingly, if activation of the PFC during the TP task was found with MEG, it was to be investigated further.

(2) Material and methods

(2.1) Participants

Twenty-nine participants completed the study: 16 controls (14 male) and 13 patients diagnosed with schizophrenia (13 male). Of the participants, three controls' data (all males) were not included in analyses due to MEG data loss for two of them and improper training procedures for one of them. Twenty-five participants included in the analyses were right-handed; one patient was left handed. All patients were chronically ill and were outpatients who had been stable on either typical (1 on stelazine) or atypical (2 on aripiprazole, 1 on olanzapine, 1 on risperidone, 2 on quetiapine, and 6 on clozapine) antipsychotic medications for at least 3 months. The patients were recruited from the outpatient clinic at the University of New Mexico Health Sciences Center. A Psychiatrist at the clinic referred patients who were diagnosed with schizophrenia and were judged stable and appropriate for the study. Participants were administered the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV SCID–Clinician Version; First et al., 1996) by a trained Research Assistant, who was supervised by either J.R.B. or F.M.H.. The DSM-IV SCID was administered to patients to verify their diagnoses of schizophrenia, with no other psychiatric dysfunction within the last 12 months. Controls received it in order to determine that they had no psychiatric dysfunction. Both patients and controls had: 1) no history of head injury with loss of consciousness for more than 5 minutes; 2) no hospitalization in the previous 3 months; 3) age 20-60; 4) no history of neurological problems; and 5) signed informed consent. Patients and controls were matched on age ($t(1,24) = -1.31$, $p = .203$; controls: $M = 33.0$ years, $SD = 9.2$; patients: $M = 37.9$ years, $SD = 9.7$) and education ($t(1,24) = 1.57$, $p = .130$; controls: $M = 14.3$ years, $SD = 2.3$; patients: $M = 13.0$ years, $SD = 2.0$). Participants' structural MRIs were read as normal 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.

(2.2) Procedures

(2.2.1) TP and Elemental Task Training—Participants were trained on all four tasks (verbal and nonverbal TP versions and their elemental counterparts) before undergoing MEG. 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 180 trials. Stimuli for the TP and elemental nonverbal versions consisted of three different abstract black and white pictures, unique in appearance for each of the tasks (see Figure 1, a and c). Stimuli for the TP and elemental verbal versions consisted of three pronounceable non-words for each task (see Figure 1, b and d). There has been evidence of less reliance on hippocampus as stimuli and their relations become more meaningful (Doeller et al., 2005; Moses et al., 2008, 2009), with patients diagnosed with schizophrenia not showing a behavioral deficit on the TP relational task that uses meaningful stimuli (Hanlon et al., 2005; Rowland et al., 2010). Although this idea has not been completely supported, with some believing the perirhinal cortex involved in familiarity (Diana et al., 2007), as a precaution stimuli and their relations were chosen to be as meaningless as possible in the present study. Presentation stimulus software version 9.9 (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. 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 versions, A is correct when presented with B. B is correct when presented with C. C is correct when presented with A. For the elemental versions, D is always correct and F is never correct. For all of the tasks, each pair of stimuli was presented until the participant responded or until 10 s had passed. The response was followed by a feedback tone, high-pitched if correct and low-pitched if not correct. There was a 3 s inter-stimulus interval (ISI) from button press or end of the 10 s window until the next stimulus onset.

Abstract pictures and pronounceable non-words were chosen to be meaningless. There is always a chance that participants will attach meaning to the stimuli and the relationships between them. Also, stimuli were chosen for the nonverbal tasks so that there is no obvious name to give them. However, participants may still attempt to verbally label nonverbal stimuli. Therefore, after MEG data collection, they completed a questionnaire that addressed the relationships between the stimuli used in the verbal and nonverbal TP and elemental tasks, difficulty level of the tasks, and finally whether participants named each of the stimuli. This was done in order to assess whether groups differ in encoding of the stimuli and their relationships to one another (creating meaning for them) for each of the tasks.

(2.2.2) MEG and behavioral testing procedures—After training on all four tasks, participants were run again on each task during collection of MEG data at the Mind Research Network MEG facility. The presentation, including the order of the tasks and instructions, were the same as in the training phase. The only difference was that the stimuli

were presented on a rear projection screen using a digital LCD projector (SANYO, Model PLC-XP41), and the MIND Input Device (Michael Doty, The Mind Research Network) replaced the mouse. The stimuli spanned a visual angle of 10°. Auditory feedback was presented to the participant through earphones (ER-3A, Etymotic Research Inc.). Participants performed each task within the MEG until approximately 200 correct trials were collected. MEG signals were collected in a magnetically and electrically shielded room (VAC Vacuumschmelze GmbH) using a whole-cortex 275-channel CTF system (VSM MedTech Ltd.). Before the participant was put under the MEG array, three coils were attached to the participant's head, one at the nasion and one at each preauricular point. These coils allowed determination of the position of the participant's head before and after the run relative to the position and orientation of the MEG sensors. Two bipolar channels of electro-oculogram (EOG) were collected, one vertical and one horizontal. Also, two cardiac leads were placed on the participant's chest, one on each side. Electrode impedances were maintained below 10 K . MEG data was collected at a sampling rate of 600 Hz, DC coupled with a lowpass filter at 150 Hz. The data also contained signals from compensation sensors located further away from the head to allow compensation for external magnetic noise sources using virtual third-order gradiometers in the analysis. Continuous raw data were collected and stored. These data were cleaned and averaged using VSM-CTF software. Trials were rejected when a blink was detected in EOG or if magnetic activity greater than 3000 fT peak-to-peak occurred in any MEG channel. In addition, only trials with correct responses were included in the average.

MEG data were analyzed with the standardized Low Resolution Electromagnetic Tomography (sLORETA; Pascual-Marqui, 2002; Wagner et al., 2004) approach in CURRY software (V6.0.12; Neuroscan). sLORETA is a weighted L2 minimum-norm approach that seeks the solution that minimizes prediction error in the least-squares sense and simultaneously minimizes power of the currents across an entire grid of a large number of fixed dipoles representing the brain (in our case, based on a 3-D grid, with points spaced 5 mm apart). In the sLORETA approach, the solution is normalized by its estimated variance to convert it into a unitless test statistic (Congedo, 2006). sLORETA analyses used a linear bandpass filter of 2 to 50 Hz (transition bandwidths 0.2 and 5 Hz), a noise level defined as 100 to 10 ms before stimuli onset, and a BEM-head model. A linear baseline of 200 to 100 ms before stimuli onset and 700 to 800 ms after stimuli onset was used. The time epoch analyzed was from 0 to 700 ms after stimulus onset. The top five percent (clipped below 95%) of the sLORETA results were examined to ensure that we only included the solutions that best explained the data. Source waveforms were generated from the sLORETA results for each region of interest (ROI; hippocampus and PFC) by first placing the cursor in the center of the strongest sLORETA activation within the ROI on the MRI, and then second using the Cursor-Guided Current Density Reconstruction (CDR) Dipole Determination feature within the CURRY software. This feature retrieves the cursor position, uses its closest CDR source location plus its CDR source strength as a function of time (sLORETA value), and source normalizes it to create a dipole. The waveform of this dipole was used to determine source strength at the same latency the ROI was activated. This source strength and latency were used for group (controls and patients), task (TP and elemental), version (verbal and nonverbal), and hemisphere (right and left) comparisons. To further examine the

response pattern of hippocampal sources during both TP versions, waveforms were averaged across participants for each group and hemisphere.

(2.2.3) MRI procedures—High-resolution T1 [TE (echo time) = 4.76 ms, TR (repetition time) = 12 ms, 20° flip angle, number of excitations (NEX) = 1, slice thickness = 1.5 mm, FOV (field of view) = 256 mm, resolution = 256 × 256] and T2 [TE = 64 ms, TR = 9000 ms, 180° flip angle, NEX = 1, slice thickness = 1.8, FOV = 256 mm, resolution = 256 x 256] anatomic images were collected with an eight-channel coil on a 1.5 Tesla Siemens Sonata scanner.

(2.2.4) Statistical Analyses—A repeated-measures analysis of variance (ANOVA) using Task (TP and elemental) and Version (verbal and nonverbal) as within-participant variables and Group (patients and controls) as the between-participants factor was performed for each of the behavioral measures (number of trials to meet criterion and percent correct during the MEG session). As was done in the Hanlon et al. (2005) study, in order to examine group differences in the lateralization of the hippocampal and PFC ROIs, two continuous asymmetry scores were computed based on left- and right-source strength and latency, using the adjusted score: right-hemisphere value minus left-hemisphere value/right-hemisphere value plus left-hemisphere value. (This laterality metric provides some scaling of the laterality difference by the magnitude of each participant's source strength and latency scores. It is a common though imperfect metric, as discussed by Davidson et al., 1990). When no satisfactory hippocampal activation was found, source strength and latency were assigned a value of zero. For all neuroimaging measures (asymmetry scores, source strength and latency) found during each Task (TP and elemental) and ROI, an ANOVAs were conducted using Version (verbal and nonverbal) as the within-participant variable and Group (patients and controls) as the between-participants factor. Right and left source strength and right and left source latency were examined separately for group differences due to having a small number of participants exhibiting bilateral activation during any one task or ROI.

(3) Results

(3.1) Behavioral Findings

(3.1.1) TP and elemental tasks—As predicted, patients performed worse on both TP versions than did controls, with no behavioral impairment seen on the control elemental versions. Behavioral data were not saved for one control participant during training, thus behavioral analyses for number of trials to reach criterion was performed on 13 patients and 12 controls.

Number of trials to reach criterion varied as a function of both Task, $F(1,23) = 13.35$, $p = .001$, and Group, $F(1,23) = 4.74$, $p = .040$, with a trend for Group × Task, $F(1,23) = 3.37$, $p = .080$ (see Figure 2a). Both groups required more trials to reach criterion for the TP versions than for the elemental versions. Patients tended to require more trials to reach criterion than controls did for both the verbal, $t(1,23) = -1.96$, $p = .062$, and nonverbal, $t(1,23) = -2.06$, $p = .051$, TP versions, with no differences found for the verbal and nonverbal versions of the elemental task. No effects involving Version reached significance.

Percent correct during the MEG session showed effects for Task, $F(1,24) = 12.80$, $p = .002$, Group, $F(1,24) = 5.97$, $p = .023$, and Group × Task, $F(1,24) = 4.71$, $p = .040$. As expected, patients performed worse (lower percent correct) during the MEG session than did controls for the verbal, $t(1,24) = 1.94$, $p = .065$, and nonverbal, $t(1,24) = 2.12$, $p = .044$, TP versions, with no differences found for the verbal and nonverbal elemental versions (see Figure 2b). No effects involving Version reached significance. Therefore, as predicted, patients had a behavioral deficit on both TP versions.

(3.1.2) Questionnaire data—Two control participants did not receive the questionnaire, so their data could not be included in the following comparisons. Using a chi-square analysis for each task, there were no differences in the number of patients vs. controls who could correctly self-report all three stimulus relationships (nonverbal TP: Patients = 11, Controls = 10; verbal TP: Patients = 11, Controls = 11; nonverbal elemental: Patients = 12, Controls = 11; verbal elemental: Patients = 11, Controls = 11). Participants were asked to rank all four tasks in difficulty, with 1 being the easiest and 4 being the most difficult. A Group × Task × Version ANOVA examined these self-report ratings. The TP task versions were reported to be more difficult to perform than were the elemental task versions, $F(1,22) = 13.88$, $p = .001$, and the verbal versions of both tasks were described as more difficult than the nonverbal versions, $F(1,22) = 4.49$, $p = .046$. Importantly, there was no group difference in reported task difficulty nor any interactions. Finally, participants reported whether they named each of the stimuli. This was examined using a chi-square analysis for each task. More controls were found to name at least one stimulus per task than did patients for the nonverbal TP (Patients = 9, Controls = 11; $\chi^2(1) = 4.06$, $p = .044$) and the nonverbal elemental task (Patients = 5, Controls = 9; $\chi^2(1) = 4.61$, $p = .032$), but no differences were found for the verbal TP (Patients = 9, Controls = 6) and elemental (Patients = 8, Controls = 6) tasks.

(3.2) Nonhippocampal Activation

During the verbal and nonverbal TP and elemental tasks, early-latency sLORETA sources localized to primary visual cortices in both groups, as expected. In addition, activation was detected in secondary visual cortical areas and in the ventral and dorsal streams involved in processing visual information. Group differences in this activation were not examined, and these neural sources will be not considered further here.

(3.3) Hippocampal Activation

(3.3.1) TP versions—Hippocampal activation was examined from 50 to 700 ms after stimulus presentation. If more than one hippocampal source based on location in each subject's structural MRI was found in the same hemisphere, waveforms were examined to determine whether they were similar in shape. In all of these cases, the waveforms were considered similar, so the hippocampal source that showed sLORETA activation closest to 400 ms was chosen for latency and strength analyses. This 400 ms latency was chosen based on hippocampal activation latency found during the TP task (Hanlon et al., 2005), an N400 component recorded from depth electrodes in both right and left hippocampi during declarative recognition memory tasks (Halgren et al., 1994), and an MEG M400 component that has been shown to localize to the mesial temporal area, as well as superior temporal and

inferior parietal areas, during auditory processing tasks (Nishitani et al., 1998, 1999). Table 1 lists the number of participants who showed right, bilateral, and left hippocampal activation for each of the tasks. Goodness-of-fit was examined for each hippocampal source using a variance measure related to signal-to-noise transformed data from the CDR dipole analysis done in CURRY. Both groups were determined to have goodness-of-fit for hippocampal sources above 77%. Figure 3 displays hippocampal activation found with sLORETA for one control and one patient during TP versions. Some participants showed a double peak within their hippocampal waveform. We investigated whether there was a group difference in the occurrence of this double peak. Four of nine controls and three of eleven patients showed a double peak in their left hippocampus during verbal TP. Four of nine controls and three of six patients showed a double peak in their right hippocampus during nonverbal TP.

As was done in the Hanlon et al. (2005) study, in order to examine group differences in the lateralization of the hippocampal source, two continuous asymmetry scores were computed based on left- and right-source strength and latency (see Statistical Analyses section). Illustrated in Figure 4, ANOVA yielded Version effects (source strength score: $F(1,20) = 8.94$, $p = .007$; latency score: $F(1,20) = 4.58$, $p = .045$) and Group × Version interactions (source strength score: $F(1,20) = 8.38$, $p = .009$; latency score: $F(1,20) = 5.73$, $p = .027$), with no overall Group effect. Control participants exhibiting a mean positive (right-lateralized) value for both source strength and latency laterality indices for the nonverbal TP version vs. a mean negative (left-lateralized) value for both source strength ($t(9) = -3.26$, $p = .010$) and latency laterality indices ($t(9) = -2.28$, $p = .049$) for the verbal TP version (see Table 2). In contrast, patients did not show this difference in laterality scores for either verbal or nonverbal TP versions. They exhibited negative (left-lateralized) values for both versions.

There were no group differences found for latency or source strength of hippocampal sources in the right or left hemisphere for either the verbal or nonverbal TP versions (see Table 3 for mean values). Thus, importantly, other group effects were not due to patients having smaller sources and thus worse signal-to-noise ratios.

Group averaged waveforms for each hemisphere were created for each TP version in order to further examine lateralized hippocampal response patterns. Figure 5 illustrates these averaged waveforms. For the nonverbal TP task, control participants showed a sustained response between 430 and 500 ms in the right hippocampus, which was not found in the left hippocampus, or in either hippocampi in patients. In contrast, for the verbal TP task, control participants showed a response, peaking around 488 ms, in the left hippocampus, which was not found in the right hippocampus, or in either hippocampi in patients. These waveforms clearly exhibit a lateralized hippocampal response pattern that differs by group and TP version.

(3.3.2) Elemental versions—Table 1 lists the number of controls and patients who showed right, bilateral, and left hippocampal activation for the verbal and nonverbal elemental versions. Both groups were determined to have goodness-of-fit values for hippocampal sources above 78%. ANOVA on asymmetry scores yielded no effects for

Group (source strength score: $F(1,18) = 1.05$, $p = .319$; latency score: $F(1,18) = 0.27$, $p = .607$), Version (source strength score: $F(1,18) = 0.84$, $p = .372$; latency score: $F(1,18) = 1.66$, $p = .214$), or the Group × Version interaction (source strength score: $F(1,18) = 2.87$, $p = .107$; latency score: $F(1,18) = 0.87$, $p = .363$). Table 2 lists mean values for each laterality score. Examining right and left hippocampal source strength and latency, resulted in only one significant group difference. For the nonverbal elemental task, patients were found to have earlier left hippocampal activation than controls, $t(16) = 2.71$, $p = .015$ (see Table 3 for mean values).

(3.4) Prefrontal Cortex Activation

(3.4.1) TP versions—Table 4 lists the number of controls and patients who showed right, bilateral, and left PFC activation (Brodmann's Areas 9, 10, 46) for the verbal and nonverbal TP versions. Both groups were determined to have goodness-of-fit values above 61%. Asymmetry scores were computed. A Group effect for the latency laterality score, $F(1,13) = 5.71$, $p = .033$, reflected patients having more leftward lateralization during TP than controls, who were right-lateralized (see Table 5 for mean values). This was also seen in a marginal Group effect obtained for the source strength laterality score, $F(1,13) = 3.72$, $p = .076$. This effect did not vary with task version (Group × Version: laterality score, $F(1,13) = 0.38$, $p = .551$; strength score, $F(1,13) = 0.14$, $p = .715$). There was no overall Version effect for either latency, $F(1,13) = 0.29$, $p = .603$, or strength, $F(1,13) = 0.26$, $p = .617$. Thus, patients exhibited more left PFC activation for both TP versions than controls did, with controls showing more right than left PFC activation. Figure 6 displays PFC activation found with sLORETA for one control and one patient during the verbal and nonverbal TP versions.

Examining right and left hemisphere PFC source strength and latency (see Table 6 for mean values) during TP resulted in only one group difference: during nonverbal TP, the left hemisphere PFC source was stronger in controls than patients, $t(11) = 3.19$, $p = .009$. However, there were only four controls showing this activation compared to nine patients.

(3.4.2) Elemental versions—Table 4 lists the number of controls and patients who showed right, bilateral, and left PFC activation for the verbal and nonverbal elemental versions. Both groups were determined to have goodness-of-fit values above 72%. ANOVA on asymmetry scores yielded no significant effects for Group (source strength score: $F(1,14) = 0.71$, $p = .414$; latency score: $F(1,14) = 1.09$, $p = .314$), Version (source strength score: $F(1,14) = 0.01$, $p = .943$; latency score: $F(1,14) = 0.23$, $p = .640$), or the Group × Version interaction (source strength score: $F(1,14) = 0.80$, $p = .386$; latency score: $F(1,14) = 1.26$, $p = .280$). Table 5 lists mean values for each laterality score. Analyses for right and left hemisphere PFC source strength and latency resulted in no group differences for source strength and latency.

(4) Discussion

Schizophrenia patients exhibited predicted deficits in hippocampal-dependent behavior and lateralization of activation in this study. Patients took more trials to learn and performed worse during the MEG scan on the verbal and nonverbal TP versions, yet did not show a

decrement in performance on the verbal and nonverbal versions of the non-hippocampal-dependent elemental task. This is a replication of the Hanlon et al. (2005) nonverbal TP results, with the extension of the deficit to verbal TP. In addition, patients exhibited less lateralized hippocampal activation than did control participants during TP. Based on a laterality score computed from each participant's hippocampal source strength and latency during both versions of the TP task, control participants showed right hippocampal activation during nonverbal TP (replicating Hanlon et al., 2005) and left hippocampal activation during verbal TP (the first test of this). This lateralized hippocampal activation was not seen in patients, who instead showed more bilateral or left hippocampal activation for both TP versions. In addition to lateralized hippocampal activation, PFC activation was observed, in line with other neuroimaging studies using the TP task (Meltzer et al., 2008; Moses et al., 2009). Overall, present results demonstrate the capacity to discriminate right and left hippocampal function via MEG and confirm a bilateral hippocampal-dependent behavioral and activation deficit in schizophrenia.

Unlike in the rat literature, which describes a non-hemispheric specialization for place learning (Kolb et al., 1984; Port et al., 2000), in humans the right hippocampus is thought to specialize in visuo-spatial ability (Burgess et al., 2002; Smith and Milner, 1981, 1989) and the left hippocampus in either verbal/narrative or episodic memory (Burgess et al., 2002; Frisk and Milner, 1990). Assessing three-dimensional allocentric visuo-spatial ability in humans has been accomplished with virtual spatial environments that require self-motion during the collection of neuroimaging data. Using positron emission tomography to examine rCBF changes, Maguire and colleagues conducted a series of studies of navigation through a virtual-reality town, finding both hippocampi activated during spatial navigation in controls, although only right hippocampal activation was associated with accurate navigation (Hartley et al., 2003; Maguire et al., 1996b, 1998). In contrast, verbal memory as a broad ability has been assessed in patients with unilateral mesial temporal lobe damage in different ways, e.g., recall of story content (Milner, 1958; Frisk and Milner, 1990; Sawrie et al., 2001), paired associative learning (Saling et al., 1993), acquisition, retrieval, and recognition memory for words (Baxendale, 1997; Martin et al., 2002). In those studies it was the left hemisphere, not the right, associated with a deficit. Using fMRI, Stark and Squire (2000) found left hippocampal activity during word recognition and bilateral activity during object recognition. This lateralization has also been found in other neuroimaging memory encoding studies (Kelly et al., 1998; Wagner et al., 1998).

Burgess et al. (2002) proposed that the left hippocampus is needed for episodic or autobiographical memory set in time and space, and they regarded verbal involvement as not essential for left hippocampal reliance. Thus, Spiers et al. (2001) investigated unilateral temporal lobectomy patients' visuo-spatial and episodic memory using a virtual-reality town to assess lateralized hippocampal function. Patients with right temporal lobectomy were impaired on the navigational measures compared to controls, and patients with left temporal lobectomy exhibited a deficit for the episodic memory measures. This study illustrates a lateralized deficit for each task and dissociates the two hippocampi. However, the episodic memory test may rely more on verbal material than the spatial memory test. This difference could be due merely to both tasks relying on relations of cues, with the spatial relying more on nonverbal cues and the episodic portion more on verbal cues. In fact there is some

evidence that patients with unilateral hippocampal damage manifest allocentric spatial deficits, regardless of the hemisphere of damage (Astur et al., 2002; Maguire et al., 1996a) and that episodic memory function does not always lateralize to one hippocampus (Ryan et al., 2001; Viskontas et al., 2000). Therefore, it is possible that the relational/configural aspect needed to perform spatial and episodic memory tasks is the important hippocampal-dependent aspect and that the use of relationships between nonverbal cues vs. verbal cues would reveal hippocampal lateralization rather than the visuo-spatial vs. episodic distinction. Results from the Hanlon et al. (2003, 2005) studies and the present study support this idea, finding right hippocampal activation during a nonverbal relational TP version and left hippocampal activation during a verbal relational TP version in controls.

Unlike controls' lateralization of hippocampal activation, patients activated left hippocampus for both verbal and nonverbal TP. This result can be interpreted as the left hippocampus trying to compensate for a right hippocampal deficit, using a verbal strategy, although inefficiently, and the right hippocampus unable to do the same for the left deficit. Another possible explanation is that the left hippocampus is over-active in schizophrenia. This explanation is interesting in light of the PFC activation pattern seen here, with patients seeming to activate the left PFC during both TP versions, in contrast to controls activating the right PFC. Thus, patients are exhibiting signs of hyperactivation of both PFC and hippocampus in the left hemisphere.

Taking advantage of the temporal resolution of MEG, the latency of hippocampal activation found with the sLORETA analysis was examined as a function of groups and tasks. There were no differences seen in hippocampal source latency. However, when the waveforms were examined by averaging across participants for each hemisphere by group, there was a clear response difference between groups and TP task versions (Figure 5). There is one waveform with a pattern that stood apart from the rest for each version of TP, the controls' right hippocampus for the nonverbal TP task and the controls' left hippocampus for the verbal TP task, both occurring around 400 to 500 ms after stimulus onset. This response pattern was not found in the contralateral hippocampus, nor was it found in patients for either hemisphere or TP version. Although there were no latency differences for the hippocampal source, these waveforms clearly exhibit a lateralized hippocampal response pattern that differs by group and TP version.

Although elemental tasks are not dependent on the hippocampus according to rat (Alvarado and Rudy, 1995a; Driscoll et al., 2005) and human hippocampal lesion studies (Rickard and Grafman, 1998; Rickard et al., 2006), hippocampal activation was still found during the performance of the task by both controls and patients. This was the case in the Hanlon et al. (2005) study as well. As others have discussed (Buckner et al., 2008; Moses and Ryan, 2006; Stark and Squire, 2001; Tesche and Karhu, 2000), neuroimaging-assessed activation of the hippocampus during a task does not necessarily imply that the structure is essential for the performance of that specific task. Moses and Ryan (2006) point out that hippocampal activation may be found for different modes of processing, as its function is to produce relational representations, even if doing so is not required for task performance (Cohen and Eichenbaum, 1993). Thus, finding hippocampal activation during the elemental task does not mean that this activation is required for performance. In addition, present findings of a

lack of lateralization of hippocampal activation during the elemental task suggest a difference in the hippocampal activation pattern seen during the elemental and TP tasks.

Future studies would benefit from a comparison of verbal and nonverbal TP task performance with clinical symptoms, everyday functional abilities, and neuropsychological performance on tests of visuo-spatial and episodic memory. Another issue is that the present sample size, as well as that in Hanlon et al. (2005), has been sufficient in power to examine behavioral performance and lateralization, but a larger sample size is needed to fully describe and explore group and TP version differences in hippocampal source strength and latency between hemispheres. Lastly, there is potential for this paradigm to be used to investigate issues of PFC and hippocampal connectivity in schizophrenia, as the task activates both structures, relying on working and relational memory integration.

(5) Conclusions

Present results suggest that by using a selective hippocampal task like TP and varying its verbal reliance, noninvasive neuroimaging can dissociate the function of the two hippocampi on a group basis. This assessment of lateralized hippocampal function has provided evidence supporting bilateral hippocampal impairment in schizophrenia. This finding illustrates the potential usefulness this technique could have for evaluating lateralized hippocampal function in other clinical populations.

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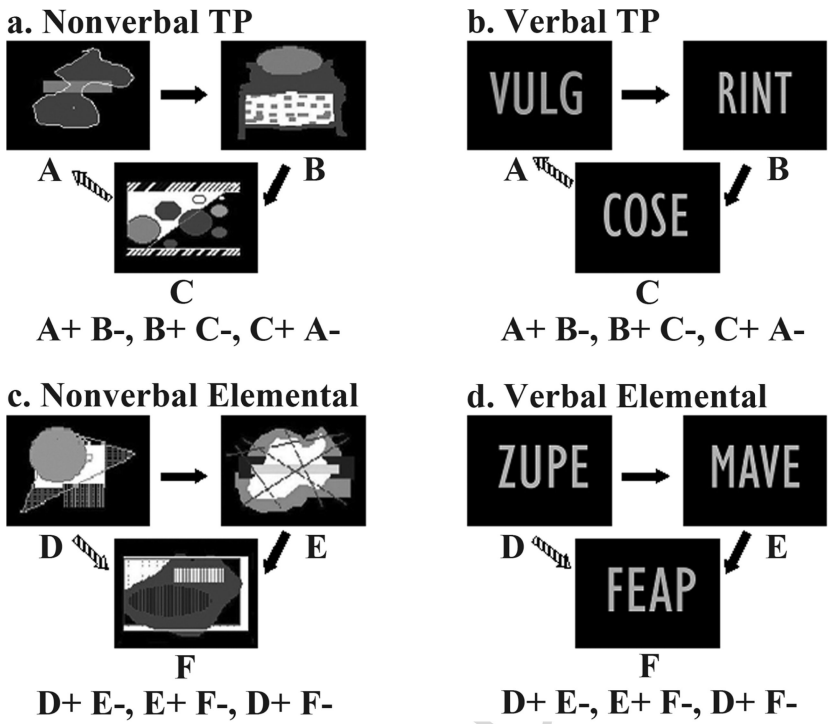


Figure 1.

Stimuli and their relationship to one another for each of the tasks conducted. Each stimulus was given a letter, for this illustration only, in order to show the relationship between the pairs, outlined beneath each task. The correct stimulus in each pairing is indicated with a "+", and the incorrect stimulus is indicated with a "−". The striped arrows indicate the difference between the stimuli relations used in the TP task versions versus those used in the elemental task versions.

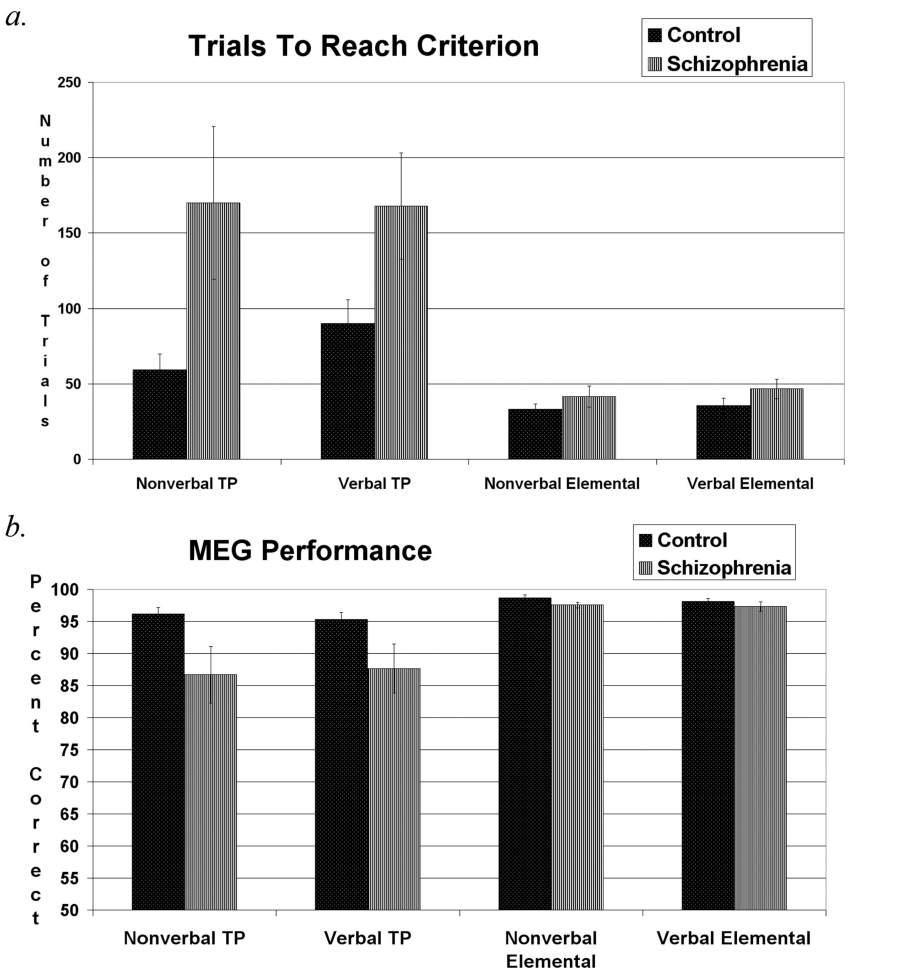


Figure 2.

TP and elemental task performance for schizophrenia and control participants for (a) number of trials to reach criterion (18 consecutive trials in a row correct) and (b) mean percent correct during the MEG session. Error bars indicate *SD*. Patients took more trials to reach criterion and performed worse within the MEG compared to controls for the verbal and nonverbal TP task, but not for the elemental task.

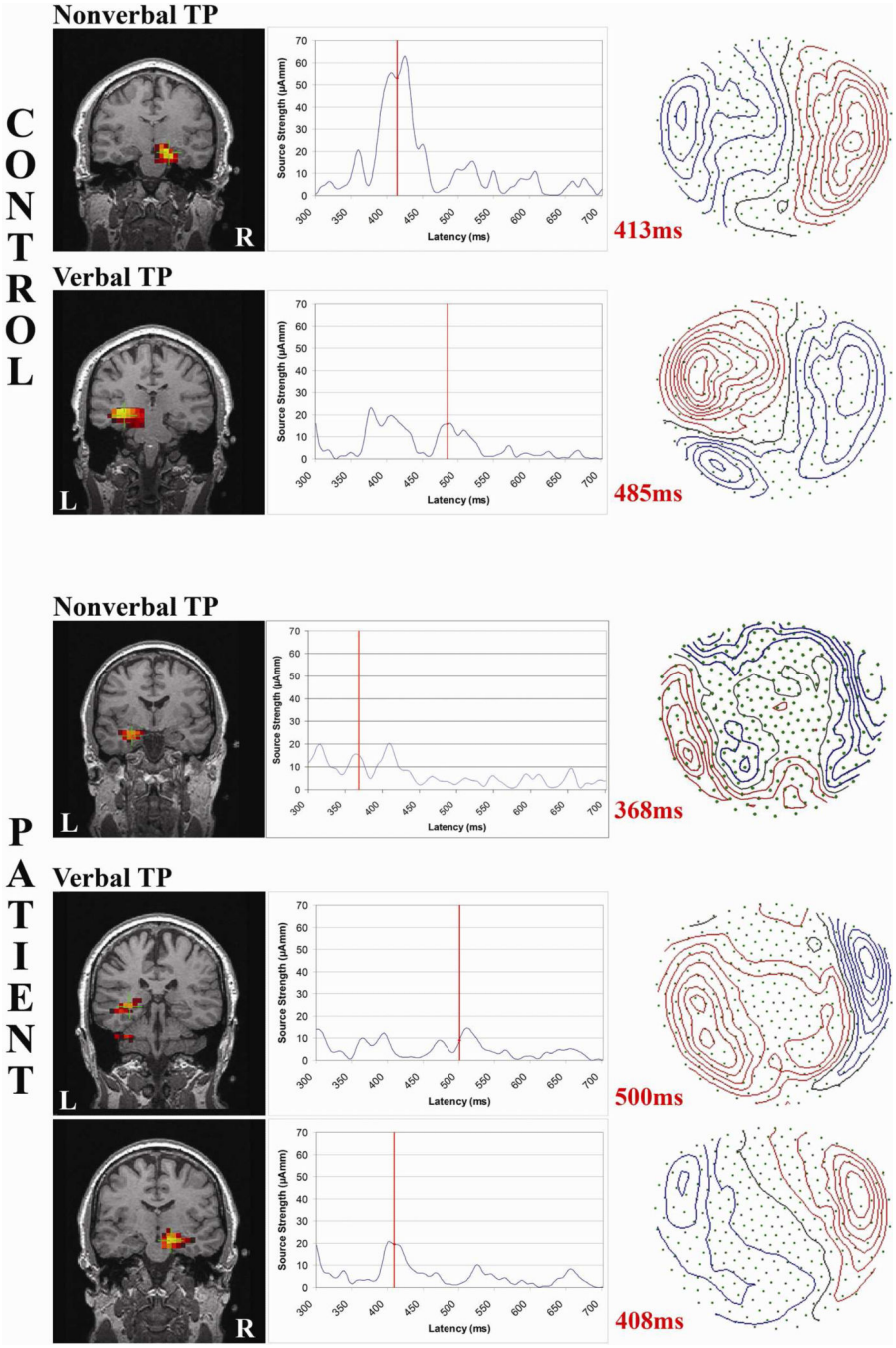
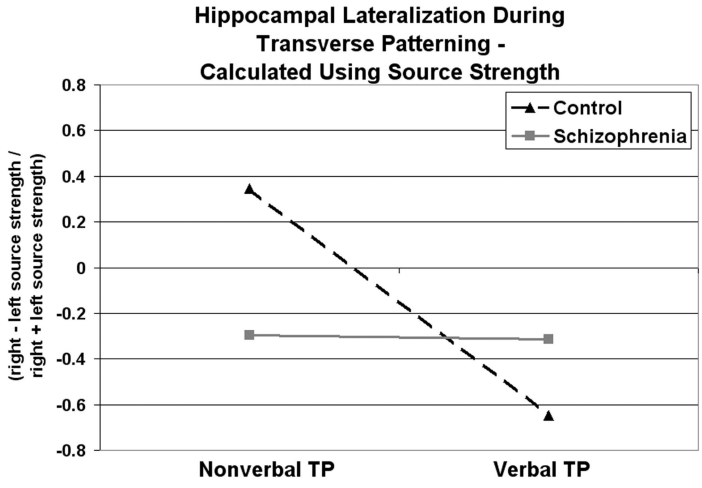


Figure 3.

Hippocampal activation (shown in color) from the sLORETA analysis is plotted on one control participant's (top) and one schizophrenia patient's (bottom) MRI. These images show the most common activation pattern for that group and task. The control showed right hippocampal activation during nonverbal TP and left hippocampal activation during verbal TP. The patient showed left hippocampal activation during nonverbal TP and bilateral hippocampal activation during verbal TP. To the right of the MRIs is the waveform computed from the current density reconstruction (CDR) dipole analysis for that sLORETA

region. The vertical red line on the waveform indicates the latency of the hippocampal activation found (shown on the MRI) from the sLORETA results. The last column on the right illustrates each dipoles magnetic field contour map at that same latency. The dots indicate each of the MEG channels, with the top channels located in front of the participant's head and the bottom channels located in back of the participant's head. The red lines illustrates where the magnetic field is exiting the brain and the left lines illustrate where the magnetic field is entering the brain.

a.



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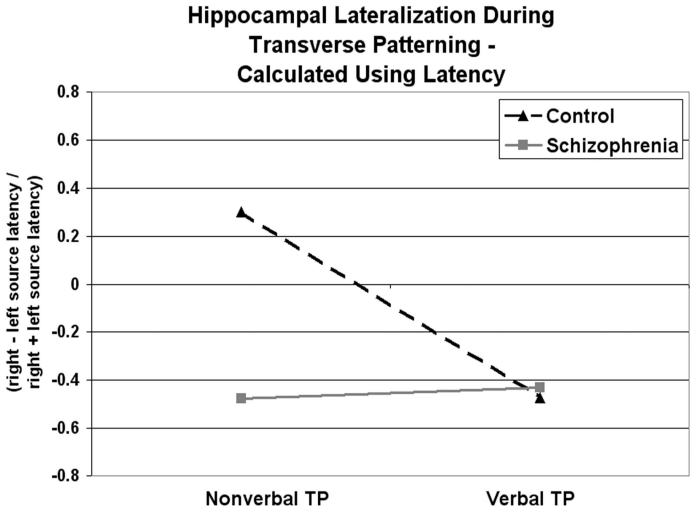

Figure 4.

The hippocampal lateralization score for each of the TP versions for control and schizophrenia patients calculated using (a) source strength and (b) latency. Both measures resulted in a significant interaction between task version (verbal and nonverbal) and group (control and patient).

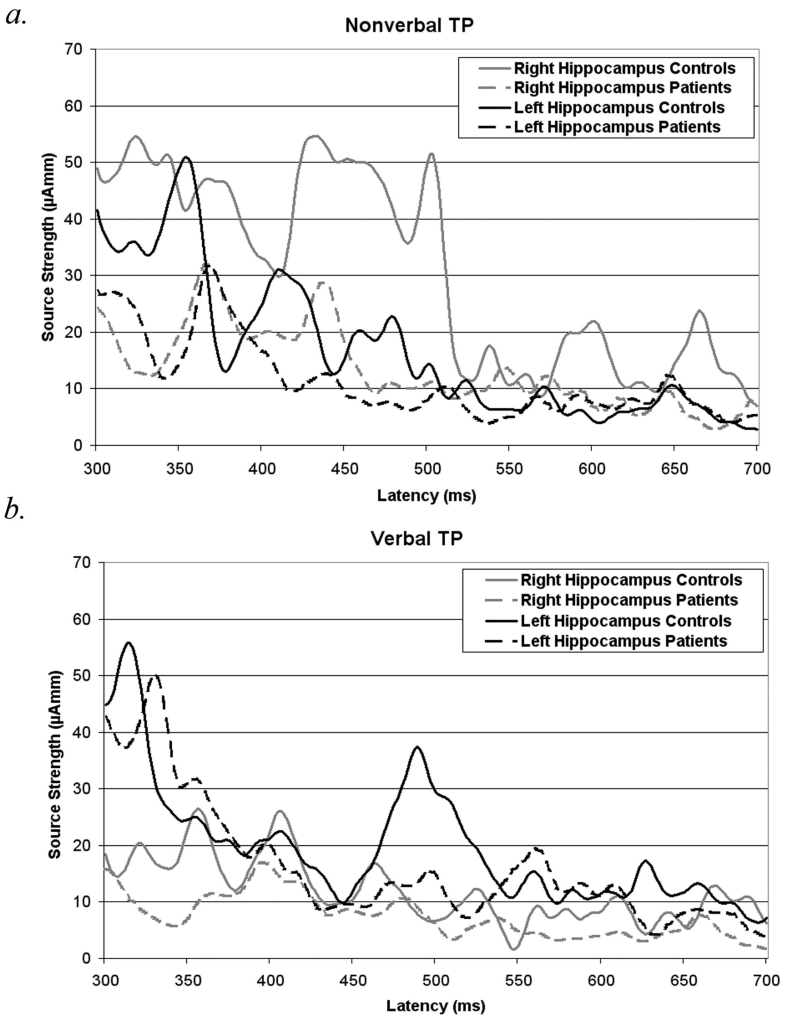

Figure 5.

For each version of TP, a) nonverbal and b) verbal, group averaged waveforms are shown for each hemisphere. For the nonverbal TP task, control participants showed a sustained response between 400 and 500 ms in the right hippocampus, which was not found in the left hippocampus, or in either hippocampi in patients. In contrast, for the verbal TP task, control participants showed a response, peaking around 500 ms, in the left hippocampus, which was not found in the right hippocampus, or in either hippocampi in patients.

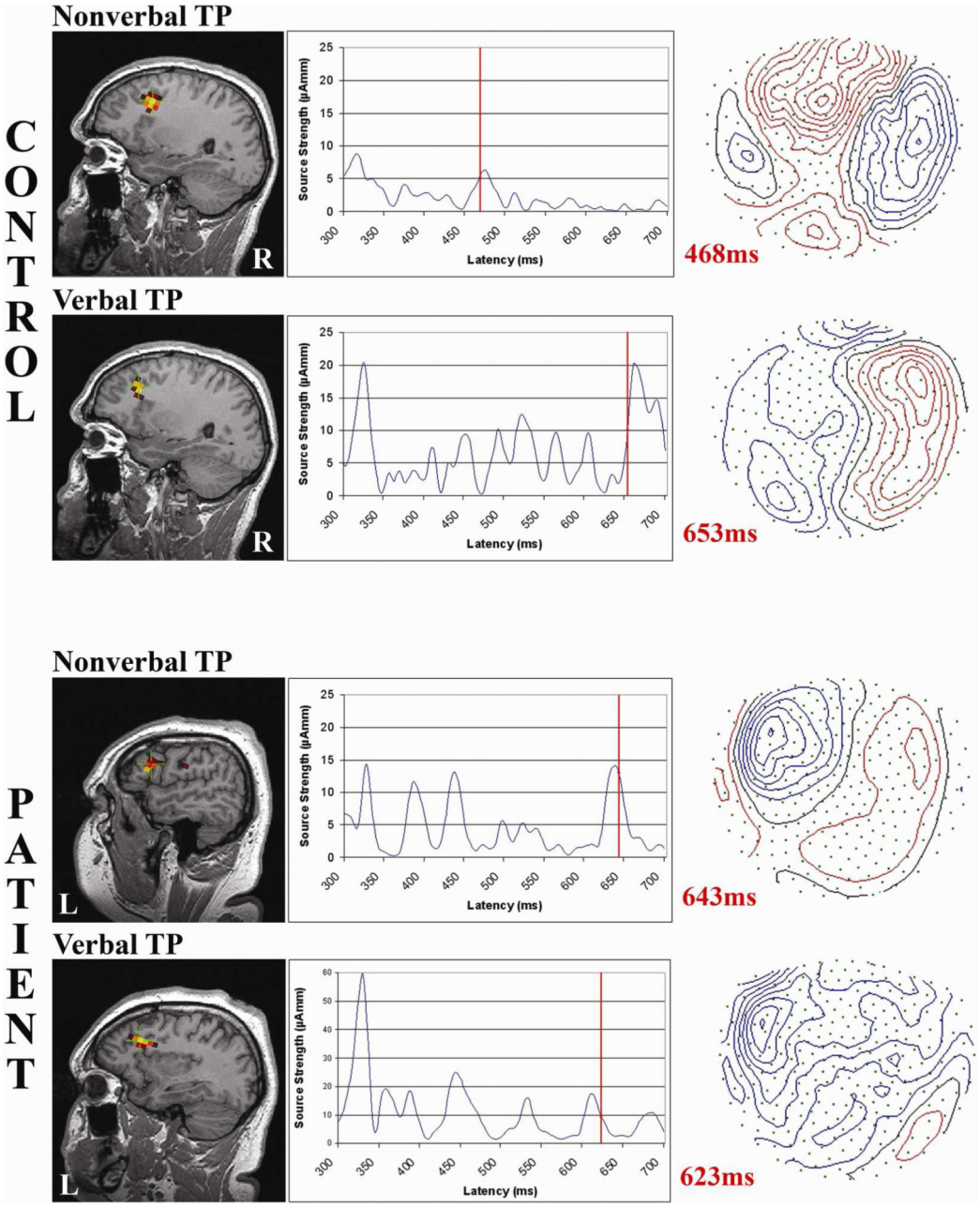

Figure 6.

PFC activation (shown in color) from the sLORETA analysis is plotted on one control participant's (top) and one schizophrenia patient's (bottom) MRI. These images show the most common activation pattern for that group and task. The control showed right PFC activation during both the nonverbal TP and verbal TP. The patient showed left PFC activation during both the nonverbal TP and verbal TP. To the right of the MRIs is the waveform computed from the CDR dipole analysis for that sLORETA location. The vertical red line on the waveform indicates the latency of the PFC activation found (shown on the MRI) from the sLORETA results. The last column on the right illustrates each dipoles magnetic field contour map at that same latency. The dots indicate each of the MEG

channels, with the top channels located in front of the participant's head and the bottom channels located in back of the participant's head. The red lines illustrates where the magnetic field is exiting the brain and the left lines illustrate where the magnetic field is entering the brain.

Table 1

Lateralized Hippocampal Activation for Patients with Schizophrenia and Control Participants

	VTP			NVTP			VEL			NVEL		
	RH	***BH***	***LH***	***RH***	***BH***	***LH***	***RH***	***BH***	***LH***	***RH***	***BH***	***LH***
Controls	1	3	6	6	3	3	1	6	6	1	5	3
Patients	1	6	5	3	3	7	2	6	2	2	4	6

Note. Number of schizophrenia patients and control participants for whom right hippocampal (RH), bilateral hippocampal (BH), and left hippocampal (LH) activation was detected during the verbal (V) and nonverbal (NV) versions of transverse patterning (TP) and the verbal (V) and nonverbal (NV) versions of the elemental task (EL).

Table 2

Mean Latency and Strength Laterality Scores for Hippocampal Activation

Task	**Latency Laterality Score**		**Strength Laterality Score**	
	Patients	***Controls***	***Patients***	***Controls***
VTP	−0.43 (.62) (N=12)	−0.47 (.74) (N=10)	−0.31 (.74) (N=12)	−0.65 (.65) (N=10)
NVTP	−0.47 (.78) (N=12)	0.30 (.82) (N=10)	−0.30 (.90) (N=12)	0.35 (.82) (N=10)
VEL	0.12 (.73) (N=10)	−0.19 (.74) (N=10)	0.00 (.76) (N=10)	−0.62 (.61) (N=10)
NVEL	−0.24 (.79) (N=10)	−0.24 (.76) (N=10)	−0.15 (.86) (N=10)	−0.09 (.77) (N=10)

Note. Mean (SD) *(N)* hippocampal source latency and strength laterality scores (right-hemisphere value minus left-hemisphere value/right-hemisphere value plus left-hemisphere value) for schizophrenia patients and control participants detected during the verbal (V) and nonverbal (NV) versions of transverse patterning (TP) and the verbal (V) and nonverbal (NV) versions of the elemental task (EL).

Table 3

Mean Latency and Strength for Hippocampal Activation

	Task	Latency		Strength	
		Patients	***Controls***	***Patients***	***Controls***
Right HP	*VTP*	362 (187) (N=7)	512 (91) (N=4)	13 (9) (N=7)	14 (6) (N=4)
	NVTP	381 (126) (N=6)	503 (109) (N=9)	38 (37) (N=6)	51 (53) (N=9)
	VEL	448 (116) (N=8)	541 (84) (N=7)	29 (31) (N=8)	41 (52) (N=7)
	NVEL	357 (128) (N=6)	385 (232) (N=6)	71 (63) (N=6)	70 (90) (N=6)
Left HP	*VTP*	501 (162) (N=11)	499 (101) (N=9)	25 (36) (N=11)	76 (124) (N=9)
	NVTP	467 (121) (N=10)	486 (147) (N=6)	23 (23) (N=10)	134 (264) (N=6)
	VEL	368 (179) (N=8)	406 (136) (N=12)	44 (63) (N=8)	113 (91) (N=12)
	NVEL	355 (116) (N=10)	514 (133) (N=8)	53 (66) (N=10)	63 (39) (N=8)

Note. Mean *(SD) (N)* right and left hippocampal (HP) source latency (in ms) and strength (in μAmm) for schizophrenia patients and control participants detected during the verbal (V) and nonverbal (NV) versions of transverse patterning (TP) and the verbal (V) and nonverbal (NV) versions of the elemental task (EL).

Table 4

Lateralized Prefrontal Cortex Activation for Patients with Schizophrenia and Control Participants

	VTP			NVTP			VEL			NVEL		
	RPF	***BPF***	***LPF***	***RPF***	***BPF***	***LPF***	***RPF***	***BPF***	***LPF***	***RPF***	***BPF***	***LPF***
Controls	4	1	4	4	2	2	4	3	2	3	2	2
Patients	2	1	7	2	1	8	3	3	4	6	0	4

Note. Number of schizophrenia patients and control participants for whom right prefrontal cortex (RPF), bilateral prefrontal cortex (BPF), and left prefrontal cortex (LPF) activation was detected during the verbal (V) and nonverbal (NV) versions of transverse patterning (TP) and the verbal (V) and nonverbal (NV) versions of the elemental task (EL).

Table 5

Mean Latency and Strength Laterality Scores for Prefrontal Cortex Activation

Task	Latency Laterality Score		Strength Laterality Score	
	Patients	*Controls*	*Patients*	*Controls*
VTP	−0.46 (.87) (N=9)	0.16 (.99) (N=6)	−0.42 (.90) (N=9)	0.16 (.98) (N=6)
NVTP	−0.48 (.87) (N=9)	0.52 (.82) (N=6)	−0.37 (.95) (N=9)	0.45 (.88) (N=6)
VEL	−0.08 (.93) (N=9)	0.60 (.50) (N=7)	−0.14 (.96) (N=9)	0.44 (.72) (N=7)
NVEL	0.11 (1.05) (N=9)	0.12 (.91) (N=7)	0.11 (1.05) (N=9)	0.15 (.93) (N=7)

Note. Mean (SD) *(N)* prefrontal cortex source latency and strength laterality scores (right-hemisphere value minus left-hemisphere value/right-hemisphere value plus left-hemisphere value) for schizophrenia patients and control participants detected during the verbal (V) and nonverbal (NV) versions of transverse patterning (TP) and the verbal (V) and nonverbal (NV) versions of the elemental task (EL).

Table 6

Mean Latency and Strength for Prefrontal Cortex Activation

	Task	Latency		Strength	
		Patients	***Controls***	***Patients***	***Controls***
Right PFC	*VTP*	575 (66) (N=3)	536 (91) (N=5)	10 (8) (N=3)	28 (22) (N=5)
	NVTP	432 (123) (N=3)	527 (45) (N=6)	30 (34) (N=3)	14 (8) (N=6)
	VEL	590 (91) (N=6)	571 (93) (N=7)	9 (5) (N=6)	26 (25) (N=7)
	NVEL	569 (153) (N=6)	500 (91) (N=5)	27 (52) (N=6)	32 (12) (N=5)
Left PFC	*VTP*	486 (138) (N=8)	548 (122) (N=5)	23 (29) (N=8)	34 (19) (N=5)
	NVTP	569 (115) (N=9)	465 (114) (N=4)	12 (5) (N=9)	20 (4) (N=4)
	VEL	544 (91) (N=7)	465 (79) (N=5)	12 (5) (N=7)	31 (25) (N=5)
	NVEL	502 (47) (N=4)	576 (70) (N=4)	13 (12) (N=4)	24 (23) (N=4)

Note. Mean (*SD*) *(N)* right and left Prefrontal Cortex (PFC) source latency (in ms) and strength (in μAmm) for schizophrenia patients and control participants detected during the verbal (V) and nonverbal (NV) versions of transverse patterning (TP) and the verbal (V) and nonverbal (NV) versions of the elemental task (EL).