Same task, different strategies: How brain networks can be influenced by memory strategy

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Abstract

Previous functional neuroimaging studies demonstrated that different neural networks underlie different types of cognitive processing by engaging participants in particular tasks, such as verbal or spatial working memory (WM) tasks. However, we report here that even when a working memory task is defined as verbal or spatial, different types of memory strategies may be employed to complete it, with concomitant variations in brain activity. We developed a questionnaire to characterize the type of strategy used by individual members in a group of 28 young healthy participants (18–25 years) during a spatial WM task. A cluster analysis was performed to differentiate groups. We acquired functional magnetoencephalography (MEG) and structural diffusion tensor imaging (DTI) measures to characterize the brain networks associated with the use of different strategies. We found two types of strategies were utilized during the spatial WM task, a visuospatial and a verbal strategy, and brain regions and timecourses of activation differed between participants who used each. Task performance also varied by type of strategy used, with verbal strategies showing an advantage. In addition, performance on neuropsychological tests (indices from WAIS-IV, REY-D Complex Figure) correlated significantly with fractional anisotropy (FA) measures for the visuospatial strategy group in white matter tracts implicated in other WM/attention studies. We conclude that differences in memory strategy can have a pronounced effect on the locations and timing of brain activation, and that these differences need further investigation as a possible confounding factor for studies using group averaging as a means for summarizing results.

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Keywords

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Introduction

If "healthy" participants of the same age group are asked to perform an identical task, it is often assumed that similar brain areas will be activated across all members of the group. Consequently, it is common in neuroimaging disciplines (e.g. fMRI, PET, ERPs) to average data over large numbers of subjects in order to make inferences about general phenomena that apply to an entire population (Faigman, 2010). However, many studies have concluded that the results of group analysis do not accurately represent the individuals that make up the group (Heun et al. 2000; Machielsen et al. 2000; Miller et al. 2002, 2009; Feredoes and Postle, 2007; Seghier et al. 2008; Seghier and Price, 2009; Parasuraman and Jiang, 2012; Aine et al. 2011). For example, Kherif et al. (2009) found that age and reading strategy were prominent sources of variability in fMRI activation for reading familiar words aloud.

Our research program has identified several potential confounds in studies of aging and memory when group averaging is used to compare young participants to a group of elders (Aine et al. 2011). For one, we find more variability within the elder group. This can in part be attributed to cardiovascular risk factors which are not typically used as exclusion criteria in aging studies, such as high blood pressure and type 2 diabetes. Thus, elder individuals with these risk factors are still considered "healthy" elderly in many aging studies.

We reported previously on the variability witnessed in data acquired from elders due to the types of health differences described above (Aine et al. 2010, 2014), and noted the additional potential confound that elders may be using different memory strategies than young individuals. Here we focus on strategy differences in a young group who are unlikely to have health issues. We reasoned that if we demonstrate the natural use of different strategies in this young homogeneous group, and corroborate that these strategies are mediated by different brain patterns (regions and timecourses of activity), then we would have strong evidence that the use of different strategies should be considered as a potential confound by neuroimaging studies of aging, and for neuroimaging studies in general that use group averaging techniques.

In this study, we used magnetoencephalography (MEG) to record functional brain activity of young healthy participants (18–25 years of age) while they were engaged in a modified Sternberg spatial working memory (WM) task. MEG is a noninvasive imaging method that measures the weak magnetic fields induced by synchronous neuronal activity. It is used to study many areas of brain function and disorders such as aging (Aine et al. 2005, 2006, 2010, 2014; Fernández, 2013), schizophrenia (Hanlon et al. 2011; Chen et al. 2013), and epilepsy (Agirre-Arrizubieta et al. 2013, Velez-Ruiz et al. 2012) with excellent temporal resolution (ms) and good spatial resolution (mm for simple activations, cm for complex activations) (Aine et al. 2012; Sanfratello et al. 2010, 2014; Supek and Aine, 1993, 1997). We hypothesized that if participants used different memory strategies to conduct the same

task, they would show different brain activation patterns at the time of recognition. For example, a verbal strategy may be used to complete a spatial location task by verbalizing to oneself "upper right hand corner" versus simply holding the location image in mind (a visuospatial strategy). Individual strategies were assessed by administering a questionnaire after the MEG session was completed. A cluster analysis was then applied to the questionnaire responses to determine the type of strategy used by each participant and to form groups, i.e. no *a priori* assumptions were made as to how many groups would be formed. Then, functional (MEG), behavioral (task performance and neuropsychological tests), and anatomical (DTI) measures were evaluated according to the cluster analysis groupings for independent corroboration that different brain networks were utilized.

Methods

Participants

A group of 28 healthy subjects (age 18–25 years, 12 male) were recruited from flyers posted at the University of New Mexico and the surrounding community. To assess health, neuropsychological tests and a neurological exam were performed for each participant. In addition, a lipid panel (i.e., high-density lipoprotein, low-density lipoprotein, total cholesterol and triglycerides), hbA1c test (average blood glucose level across 3 months), and blood pressure measurements were obtained (note: these individuals participated in a larger study on aging). The Human Research Review Committee at the University of New Mexico Health Sciences Center approved the use of human participants for this study (HRRC#06-267) and written informed consent was obtained from all subjects participating in the study.

Spatial working memory task, MEG acquisition and preprocessing

Since the ultimate goal was to determine if we could differentiate between different strategies used during a spatial task, we tested this young, homogeneous group using the spatial Sternberg WM task illustrated in Figure 1. Displays (16-cell arrays) subtended 4.0° in the central field and appeared sequentially every 1.2 s with a 2 s inter-stimulus interval and a 3.6 s delay interval. Stimulus duration was 266 ms. Some of the digits in the matrix were presented backward to avoid using 2-digit numerals. However, the digits to be remembered were always presented normally. The task had two memory set items. Participants were to respond "yes" (right index finger press) or "no" (left index finger press) if the last display (probe) contained one of the to-be-remembered items (the locations of the red digits). The total number of trials for each condition was 120 (e.g., 120 trials of "yes" it matched and 120 trials of "no" it did not match). Only the "yes" trials were used for the present study.

Participants were seated in an Elekta Neuromag 306 MEG system (306 channels, sampling rate = 1000 Hz, high pass filter = 1 Hz, low pass filter = 300 Hz) while completing the WM task described above. The task was explained and participants were given a short practice session before beginning. Tasks were performed on the same day with short rest breaks every 7–8 minutes. Those who needed corrective lenses were fitted with MEG compatible frames and lenses for the duration of the task. The MEG data were later filtered (Maxfilter,

Elekta) to minimize signals coming from outside a sphere around the brain using signal space separation (SSS) (e.g. heartbeat artifacts). Eyeblinks were suppressed separately using signal space projection (SSP) and the trials were averaged together within subject for each condition.

Immediately after the completion of the spatial WM task within the MEG scanner a structured questionnaire was administered (Likert scale). Eleven of these statements were used in a cluster analysis to determine the type of strategy each participant used during the task. This subset was specific to this paradigm (i.e., since this study was a part of a larger aging study, only questions related to this particular paradigm and the young group of participants were used).

MRI/diffusion tensor imaging (DTI) data acquisition and processing

MRI scans of the individual subjects were acquired in order to combine this structural information with the MEG results, and thus determine the locations of brain activity during the spatial WM task described above. The Siemens 3T Tim Trio was used for T1 structural and T2 scans (MPRAGE, Turbo Spin Echo, and FLAIR). T1-weighted MPRAGE sequence: 1.0 mm sagittal slices, 7° Flip angle, TR=2530 ms, TE1=1.64 ms, TE2=3.5 ms, TE3=5.36 ms, TE4=7.22 ms, TE5=9.08 ms, FOV was 256×256, 6 minutes; T2-weighted Turbo Spin Echo (TSE) sequence: 1.5 mm axial slices, 155° Flip angle, TR=13500 ms, TE1=77 ms, FOV was 220×220 with 1.5 mm slice thickness, acquisition time of ~3 minutes; and T2-weighted FLAIR sequence: 1.5 mm sagittal slices, TR=6000 ms, TE=412 ms, FOV was 256×256, acquisition time of ~5 minutes.

A DTI sequence was also acquired to determine white matter tract integrity via fractional anisotropy (FA) values. The DTI sequence had 60 directions, $b = 800$ s/mm^2 and 10 measurements of $b = 0$, for 12 min of acquisition time. The $b = 0$ measurements were interleaved after every six non-zero b-value measurements. DTI was obtained in the axial direction along the AC–PC line. The FOV was 256×256 mm with a 2 mm slice thickness, 72 slices, 128×128 matrix size, voxel size = 2 mm × 2 mm × 2 mm, TE = 84 ms, TR = 9000 ms, NEX = 1, partial Fourier encoding of 3/4, and with a GRAPPA acceleration factor of 2. Tract-based spatial statistics (TBSS) was used for the analysis (Smith et al. 2006), available in the FSL software package. DTI preprocessing consisted of the following steps: 1) gradient directions with more than 10% signal dropouts caused by subject motion were not included in further analysis; 2) motion and eddy current correction (FSL); and 3) correction of gradient directions for any image rotation done during the previous motion correction step. The scalar diffusion parameter FA was calculated using dtifit (FSL). The FA image was aligned to an FA template (normalized to the Montreal Neurological Institute brain atlas space) with a nonlinear registration algorithm, FNIRT (FMRIB's Nonlinear Image Registration Tool; FSL). A mean FA image was calculated from the set of spatially normalized images. The TBSS algorithm was applied to the mean FA image to calculate a mean white matter tract skeleton. The FA data of each subject was then projected onto this mean skeleton to obtain a skeletonized image corresponding to each subject. To examine group differences, mean FA values were calculated from the FA skeleton for the 50 white matter regions defined in the JHU-ICBM 50 region white-matter atlas included in the FSL

software package (Mori et al. 2008). Between group t-tests were computed for each of the 50 white matter regions, and were then adjusted using Benjamini and Hochberg's False Discovery Rate (FDR) procedure (Benjamini and Hochberg, 1995). FDR is the expected fraction of tests declared significant in a study in which the null hypothesis is true. FDR explicitly controls the error rate of test conclusions among significant results (Benjamini and Hochberg, 1995), and is often more appropriate than FWER corrections such as Bonferroni while retaining more power in the results (Genovese et al. 2002).

MEG data analysis

The structural MPRAGE or FLAIR MRI scan (depending on data quality) was processed within MRIVIEW software (Ranken and George, 1993) to calculate a best-fitting sphere for each individuals' head model to use with the multidipole, spatiotemporal inverse procedure CSST (Calibrated-Start Spatio-Temporal). CSST determines the best-fitting source locations for a given dataset, as well as their corresponding timecourses (Ranken et al. 2002, 2004). CSST begins with random combinations of MR-derived starting locations from within the cortical volume and uses the Nelder-Mead non-linear downhill simplex procedure to perform a spatial search (Nelder and Mead, 1965). Information based on a singular value decomposition (SVD) of the data matrix is used for determining a range for the number of sources to be localized. Fits to the data were conducted for each model order included in this range. Model adequacy was determined by assessing the reduced chi-square values associated with each model order (Supek and Aine, 1993; 1997), along with an examination of the dipole clusters to assess scatter (typically associated with overmodeling or fitting of noise) and the residual waveforms to assess whether additional signal remained (an indication of undermodeling).

After CSST was used to calculate the dipole locations and their timecourses to probe stimuli (the recognition aspect of the task) for each individual participant, the locations were converted to Talairach coordinates using a Matlab script (COORDTRANS, Uutela 2000, personal communication), to normalize the locations for each individual to the same brain space. COORDTRANS uses a 9-point affine transformation to convert from the Neuromag coordinate system to the Talairach coordinate system. The anatomical locations and distances necessary for the code are determined from individual MRIs. The required locations are the anterior commissure (AC), posterior commissure (PC), and midline; the required distances are AC to right edge of brain, AC to left edge of brain, AC to front of brain, PC to back of brain, AC to top of brain, and AC to bottom of brain. The applet at Talairach.org (Lancaster et al. 1997, 2000) was then used to identify the boundaries of medial temporal and occipital brain areas. These boundaries (+/−5mm) were then used to identify which participants revealed activities in these brain areas. Finally, the sources found in medial temporal lobe (MTL) and occipital cortex (OCC) were plotted on the "adult brain mesh" (Fang and Boas, 2009), and were color coded to reflect the type of strategy the participants used to remember spatial locations, as discussed above. Chi-squared was used to evaluate group differences in presence/absence of sources. T-tests (1-tailed, unequal variance) were conducted to determine significant differences between groups on peak amplitudes and onset latencies for the source timecourses.

Neuropsychological tests

The neuropsychological tests administered were the Rey Complex Figure Test (REY-D), California Verbal Learning Test (CVLT), and the Wechsler Adult Intelligence Scale-IV (WAIS-IV). We were interested in whether the 4 indices derived from the WAIS-IV would differ between strategy groups: working memory index (WMI—digit span and arithmetic), verbal comprehension index (VCI—similarities and vocabulary), perceptual reasoning index (PRI—block design, matrix reasoning, and visual puzzles) and processing speed index (PSI—symbol search and coding). We discuss only those that showed significant differences between groups.

Statistics for behavioral tasks

Strategy cluster groups were formed using average linkage, cluster analysis with Euclidean distances from 11 relevant Likert scale statements taken from the questionnaire which participants completed after the Sternberg WM task/MEG scan (Fig. 2). These statistics were computed by a biostatistician using SAS 9.3 (http://www.sas.com, Cary, NC).

T-tests (1-tailed, unequal variance) were computed between groups to determine if there were significant differences in: performance on the neuropsychological tests, performance on the spatial WM task (total correct and RTs), and FA values. Pearson correlations were computed between FA in white matter tracts and performance on the neuropsychological tests, as well as performance on the spatial WM task (total correct and RTs). Correlations were adjusted for Type I errors using FDR.

Results

Behavioral results

Cluster analysis—Two groups were identified by cluster analysis, based on the questionnaire data (Fig. 2), a verbal strategy group and a visuospatial strategy group. Participants were asked how strongly they agreed or disagreed (Likert scale) with particular statements. Examples of the statements used to differentiate the groups were, "I did keep the digit locations in mind the way they were presented" for the visuospatial group and for the verbal group, "To help me remember the locations of the red digits I thought of a word or phrase. For example, I thought to myself "upper left corner" or "2 o'clock." To be assured that our groups were homogeneous we present the age, health, and IQ data of the 2 groups in Table 1. No significant differences were found between groups. These results also confirm our premise that these groups of young participants were healthy individuals.

Spatial WM task—There was a significant difference in working memory performance on the spatial Sternberg WM task depending on strategy type (verbal vs. visuospatial). Performance was determined by calculating the proportion of trials the participant responded to correctly. Those participants who used a verbal strategy did better in terms of total correct on the spatial WM task (M=95%, SD=3.6), than those who used a visuospatial strategy (M=87%, SD=10), *p=0.005*. Reaction times on the spatial WM task showed no significant difference between the verbal (M=745 ms, SD=122) and visuospatial groups (M=767 ms, SD=109), with *p=0.33*.

Neuropsychological tests—The verbal group also performed significantly better than the visuospatial group on the CVLT (*p=0.046*), supporting the premise that they are better at verbal tests than the group who used a visuospatial strategy for the WM task. No significant difference in performance on any of the other neuropsychological tests was observed between the verbal and visuospatial groups.

MEG results

Figure 3 shows representative samples of averaged evoked fields for two participants when 1) using a verbal strategy to accomplish the spatial WM task (left column) versus 2) using a spatial strategy to conduct the spatial WM task (right column). The signals measured at the sensor level are shown in the top row for both participants. The forward model determined from the average of the 10 best-fitting CSST solutions is shown in the middle row. The residual variance, the difference between the measured and the modeled data are shown in the third row. Note that the residual error is small in both instances, indicating that the multidipole, spatiotemporal solutions did a good job at reconstructing the magnetic signals seen at the sensor level. Additional procedural information on the use of the CSST method can be found in Aine et al. (2010).

Distinct brain activation patterns were found that were dependent on the general memory strategy used by participants in the study, verbal or visuospatial. There were two distinct brain areas preferentially utilized whose location and timecourses depended on the strategy employed. When examining the MTL and OCC areas, we determined that many more participants using a verbal strategy evoked activity in right MTL than those who used a visuospatial strategy (Fig. 4). Eleven of 17 verbal strategists (65%) showed right MTL activity, while only 11% of visuospatial strategists did (χ^2 (1, N=26) = 4.25, *p= 0.039*). Six of the 11 verbal participants who exhibited right MTL activity also showed activity in left MTL (i.e. bilateral MTL activity). There was no significant difference in the number of participants revealing activity in left MTL between the two strategy groups. The trend was reversed for right OCC activation, with many more visuospatial strategists showing activity in right OCC, 78%, versus 29% of those using a verbal strategy (χ^2 (1, N=26) 5.13, *p=0.024*). As can be seen in Fig. 4, occasionally a participant showed 2 areas of activation (dipoles within the same brain region, e.g. MTL). We examined the locations and timecourses to determine that 1) one was not a noise source (i.e., low amplitude random timecourse activity or scatter seen across the best-fitting dipole solutions) and 2) the two sources were not actually the same source with antiparallel orientations (typically resulting in very high amplitude signals). It was determined that these additional sources were reasonable activations. For example, both anterior and posterior MTL activity was found for subject 290. Even if a subject showed two areas of activation within the same brain region they were only counted once for the chi-squared test. We found no significant difference in age between the verbal (M=21.9 years, SD=1.8) and visuospatial (M=21.4 years; SD=2.2) groups, with *p=0.29* (also shown in Table 1).

Differences between the strategy groups was also seen in the timecourses in cases where the same brain areas were activated (Fig. 5). For example, for the visuospatial group the onset of left MTL activation (green tracing in the bottom panel; M=58, SD=12) was delayed relative

to both left OCC activation (blue tracing in the bottom panel; M=50 ms, SD=20) within the visuospatial group (*p=0.05*), as well as relative to left MTL activation (green tracing in top panel; M=36 ms, SD=9) of the verbal group (*p=0.004*). We define onset latency of activity as the time at which the timecourse is greater than 3 SD of the baseline, for a minimum of 10 ms to eliminate noise-related onsets. We also show in Fig. 5 source locations and their associated timecourses for two representative individuals, one from each group (verbal and visuospatial).

Skeletal FA results

Between group results—The only significant difference in FA values between the visuospatial and verbal strategy groups, after controlling for multiple comparisons, was for the right superior cerebellar peduncle tract (SCP-R), with the visuospatial group (M=.68; SD=.01) showing higher FA values than the verbal group (M=.65; SD=.02, *p=0.001*).

FA and behavioral performance correlations—We additionally examined the relationship between FA of the participants and behavioral performance results on neuropsychological tests and on our Sternberg spatial WM task (total correct and RTs). We discuss FDR corrected results at a significance level of α<0.1, (N=50) (Table 2 orange highlighting).

First, FA of white matter tracts correlated significantly with performance on neuropsychological tests for the visuospatial group only (Table 2). REY-D, a visuospatial memory test, correlated significantly with UNC-R. In contrast, CVLT, a verbal memory test, showed no significant correlations with FA for either the visuospatial or verbal groups (not shown in the table).

WMI, an index of working memory (weighted by verbal working memory subscales on the WAIS-IV), was correlated positively with FA in the pontine crossing tract (PCT, a part of the middle cerebellar peduncle) and with the left superior fronto-occipital fasciculus (SFO-L) for the visuospatial group.

Perceptual reasoning ability is indexed by PRI. Correlations between performance on this index and FA of white matter tracts showed the greatest difference between groups, with the visuospatial group having a number of brain areas strongly correlated with performance, while the verbal group again showed no significant correlation between performance on this index and FA in any region. The FA tracts that correlated significantly with PRI for the visuospatial group were the body of corpus callosum (BCC), posterior corona radiata (PCR-R), superior longitudinal fasciculus (SLF-R), and the tapetum (TAP-R).

There was a strong correlation between BCC and RTs solely for the visuospatial group (r = .88, FDR corrected). Recall that BCC was also strongly correlated with this groups' performance on PRI (Table 2). There were no significant correlations between total correct and any white matter tracts, for either group.

The most interesting result is the number of white matter tracts that were significantly correlated with the visuospatial groups' performance on a variety of neuropsychological

tests and the spatial WM task, whereas the verbal group showed no such correlations. To provide a visual corroboration of these differences (and to determine that outliers were not responsible) we plotted behavioral performance values versus FA values for the visuospatial group where significant correlations were observed, along with the corresponding verbal group's results. An example is shown in Fig. 6, supporting the assertion that meaningful correlation differences between the strategy groups were identified.

Discussion

Strategy differences and memory performance

Young healthy participants were objectively divided into groups using a cluster analysis based on questionnaire responses provided immediately after completing a Sternberg spatial WM task. Two cluster groups resulted which were labeled as verbal and visuospatial, given the nature of the responses. The verbal group performed significantly better than the visuospatial group on both our Sternberg spatial WM task and the CVLT, a test of verbal memory. Their performance on the CVLT provides independent verification that the verbal group was better at verbal memory tasks, than the visuospatial group. Furthermore, their better performance on the spatial task suggests that a verbal strategy was more effective for this particular WM task. Although we found no statistically significant difference in age between the two groups it is possible that the cognitive maturity of the groups differed, in the sense that as individuals develop in adolescence they rely less on rote spatial rehearsal and begin to employ more verbally mediated strategies (Schweinsburg et al. 2005; Aine et al. 2011; Scherf et al. 2006). It has also been suggested that as we age we develop complex mnemonic strategies such as chunking to lessen cognitive load (Bor et al. 2003). In this case, using a verbal strategy may simply have reduced cognitive load sufficiently to improve task performance.

MEG activity

We predicted that we would find converging functional imaging data to support the clustering of participants based on the type of memory strategy individuals used. We found that both the visuospatial and verbal groups showed activation of MTL. MTL, and portions of the hippocampus in particular, have been shown to be active during WM tasks such as during a letter working memory task with and without distractors (Sakai and Passingham, 2004) and during a 15-word learning test including tasks of immediate and delayed recall in non-demented elderly (Hackert et al. 2002). MTL has also been shown to be responsive during spatial working memory tasks. Olson et al. (2006) conducted two experiments in which patients with hippocampal lesions and controls were required to remember the location of a line-drawn object within each of a series of three 3×3 matrices. The patients with hippocampal lesions showed a deficit in both studies. Furthermore, Prince and colleagues (2005) provided evidence that cortical activity related to successful encoding and retrieval of relational items was associated with MTL structures, where encoding activated anterior hippocampus and retrieval activated posterior hippocampus/parahippocampal gyrus as well as prefrontal cortices. The findings of Schacter et al. (1997) and Giovanello et al. (2009) support the notion that posterior hippocampus may mediate perceptual matching or exact reinstatement of events between study and test phases. MTL activity has also been

observed during performance of standard neuropsychological verbal WM subtests and in visuospatial WM tasks (Travis et al. 2013; Doucet et al. 2013).

In the present study, however, we found that the verbal group showed preferential activation in right MTL, which was not seen in participants who used a visuospatial strategy. Specifically, more participants showed bilateral MTL activity for the verbal group while left MTL activity was found for the visuospatial group. We reiterate that the task was a designed to be a spatial WM task, in light of these results. We also found a distinctive timecourse difference between the two groups in MTL, even when the same brain area was active – the onset of left MTL activity was delayed by approximately 50 ms in the visuospatial group relative to the verbal group. We speculate that this delay in left MTL activity could reflect the poorer task accuracy for the visuospatial group in the spatial WM task. For example, research has shown that verbal abstraction can lead to better and faster performance by conserving attentional resources (Tun et al. 1998).

As predicted, we found independent convergence of results with the imaging data showing that different functional networks mediated the different strategies each group utilized. In addition, differences in timecourses in left MTL further corroborate that different brain networks mediated these different strategies.

FA, behavioral task performance, and memory strategy

We have already shown that there are distinct differences in how the verbal group processes visuospatial and verbal information, reflected in brain activation patterns and superior performance on both the spatial WM task and CVLT, in comparison to the visuospatial group. Interestingly, only the visuospatial group showed significant correlations between anatomical locations (differences in FA in certain white matter regions) and performance on the behavioral tasks/tests. Many of these white matter regions have previously been associated with working memory and/or attention.

One of these white matter tracts is the uncinate fasciculus (UNC), a band of long association fibers connecting the frontal and temporal lobes of the cerebrum. The UNC connects parts of the limbic system such as the hippocampus and amygdala in the temporal lobe with frontal cortex (e.g., orbitofrontal cortex). It is the last white matter tract to mature in the human brain and continues to mature past 30 years of age (Lebel et al. 2008). Typically, UNC-L has been shown to have greater FA than UNC-R in studies due to left hemisphere specialization of language (Rodrigo et al. 2007). In the research presented here we find a high correlation between performance on the REY-D Complex Figure and UNC-R, for a group of individuals who have shown a preference for using a visuospatial strategy to complete memory tasks.

The high correlation between PCT and WMI for the visuospatial group is also worth elaborating, since only recent evidence has shown a role for the cerebellum in WM (recall that we also found a significant difference in FA between the verbal and visuospatial groups in SCP-R ($p=0.001$), with the visuospatial group having higher FA values). For example, the cerebellar peduncle, which includes PCT, has recently been correlated with accuracy on a verbal 2-back task indicating a role for this white matter tract in sustained attention and

working memory (Takahashi et al. 2010). Furthermore, efferents from the cerebellar nuclei project to multiple subdivisions of the ventrolateral thalamus (Percheron et al. 1996), which, in turn, project to many cortical areas, including regions of frontal, prefrontal, and posterior parietal cortex (Jones, 1985). In fact, it has been argued that the functional map of the cerebellar cortex is likely to be as rich and complex as that in the cerebral cortex (Kelly and Strick, 2003). It is also now apparent that a significant portion of the output of the cerebellum projects to non-motor areas of the cerebral cortex, including regions of prefrontal and posterior parietal cortex. Thus, the anatomy exists for cerebellar output to influence the cognitive and visuospatial computations performed in prefrontal and posterior parietal cortex (Clower et al. 2001, 2005; Middleton and Strick, 2001; Strick et al. 2009).

WMI performance also correlated significantly with FA in SFO-L. The inferior and superior fronto-occipital fasciculi (IFO/SFO) are part of the dorsal visual stream linking parieto-occipital regions with dorsolateral and frontal areas. This area has been implicated in attention and visual processing in a number of studies (Doricchi et al. 2008; Rudrauf et al. 2008).

A number of tracts also correlated with the visuospatial groups' performance on the perceptual reasoning index (PRI), including BCC, PCR-R, SLF-R, and TAP-R. Interestingly, all of these tracts, except BCC, were in the right hemisphere. We discuss each of these areas below.

BCC, in addition to significantly correlating with PRI, also significantly correlated with RTs on the Sternberg WM task for the visuospatial group. The BCC, and related cortical regions (GCC, SCC, anterior and posterior cingulate), are often tagged as a network mediating memory functions (Burgess et al. 2001; Kraus et al. 2007; Torta and Cauda, 2011). The GCC connects medial and lateral surfaces of the frontal lobes while FX provides hippocampal and parahippocampal output to the mammillary bodies (Aggleton et al. 2005; Vann et al. 2011). FX is the largest efferent pathway from the hippocampus (Koenig et al. 2013), while TAP is the continuation of the fiber tract from the corpus callosum into the cerebral white matter of the occipital lobe.

The corona radiata is a white matter sheet that contains both descending and ascending axons that carry nearly all of the neural traffic to and from the cerebral cortex. Children with higher estimates of white matter integrity in PCR were more accurate during a task of cognitive control, where cognitive control is defined as the ability to pay attention and suppress interference (Chaddock-Heyman et al. 2013), indicating a role for PCR in attentional processes.

Lastly, SLF is a major tract that connects regions of the temporal (posterior and superior) and parietal lobes with prefrontal cortex (Croxson et al. 2005). Several DTI studies have associated portions of the SLF with verbal processing and memory (Gold et al. 2007; Peters et al. 2012). For example, Karlsgodt et al. (2008) found a positive correlation between performance on a Sternberg verbal working memory task and FA in the SLF in recent-onset schizophrenics. Similarly, Peters et al. (2012) showed a significant bilateral increase in FA in the SLF with development, which correlated positively with verbal working memory

performance. And Kamali et al. (2014) demonstrated the trajectory and connectivity of the SLF fibers in relation to other language pathways using high resolution DTI. However, there may also be a role for the SLF in visuospatial attention. Thiebaut de Schotten et al. (2011) showed evidence that hemispheric specialization of part of the SLF is associated with an unbalanced speed of visuospatial processing and the amount of anatomical lateralization and degree of asymmetry of the SLF correlated with performance of visuospatial tasks. Vestergaard et al. (2011) observed a significant association between higher FA in the left fronto-parietal network and better spatial WM skills, independent of age, for a group of adolescents. The left fronto-parietal network is composed of the SLF, the regional white matter underlying the dorsolateral PFC, and the posterior parietal cortex. Finally, there is also evidence of attention orienting being dependent upon SLF function (Ge at al. 2013).

To summarize, we found significant correlations between FA and neuropsychological tests (e.g., REY-D and WMI) solely for the visuospatial group, with many of the significantly correlated white matter regions previously shown to be involved in WM/attentional tasks. In contrast, the verbal group showed no significant correlations. Therefore, our anatomical data also provides converging evidence that these two groups, verbal and visuospatial, use different brain regions to conduct memory tasks.

Conclusions

The present study provides strong evidence that different memory strategies may be employed by healthy individuals within the same age cohort, and that these strategy groups use different brain networks for completing WM tasks. Our results also indicate that when a verbal memory strategy is used for a spatial working memory task better task performance is attained. We believe this is the first demonstration of the effect of strategies on task performance and brain activity based on a cluster analysis to initially separate strategy types. The existence of strategy differences was independently corroborated by converging results obtained from behavioral task measures, in addition to functional and anatomical measures.

As pointed out by Miller et al. (2012), if neuroimaging is to be used to make inferences about an individual, then multiple dimensions on which an individual may vary from one to another must be considered (Miller et al. 2012; Aine et al. 2011). Type of memory strategy utilized certainly appears to be one of them. We are not arguing against the use of averaged data. Clearly averaging data across individuals can and has been very useful for neuroimaging research. Yet, the importance of taking into account individual differences in strategy is highlighted by our current results and, for example, by results from a study conducted by Kherif et al. (2009). Kherif and colleagues discuss how in normal populations activation in the posterior cingulate and precuneus is not consistently reported in fMRI studies of reading aloud. But they show that it is activated by a subset of subjects in their study and can be linked to a particular reading strategy (Kherif et al. 2009). Therefore the use of averaging to make inferences about a group should be done carefully, with for example, task selection chosen such that alternative strategies to perform the task are less likely to be utilized.

There is also a tendency in the literature to describe the use of atypical brain areas as "compensatory." For example, elders are typically proclaimed as somehow deficient when

they are shown to recruit additional and/or different brain areas than young to perform the same task (Cabeza, 2002). However, an alternative explanation is that different neural activation patterns sometimes seen between young and elderly groups may result from the different strategies invoked to complete a task which may evolve with age and the maturity of, for example, white matter tracts (Aine et al. 2006, 2010, 2011).

Future work in this area should include a study of individual trials and how they differ within the same individual. For example, although we looked at the tendency for an individual to use a particular strategy there is no reason to assume that this strategy was always used throughout the entire task. Therefore perhaps sorting the individual trials into categories and looking on a trial by trial basis to determine differences between those trials where it was easy to verbalize the location (e.g. "upper right hand corner") and those where it was not easy to verbalize the location may provide insight into, e.g. how consistently a strategy is used. In addition, further elaboration of an analysis of functional connectivity can provide additional insight into the uniqueness of strategies, and would be particularly interesting when individuals use different strategies with some overlap in areas of activity.

Finally, analysis of intersubject variability may be complementary to conventional analysis that averages data across individuals. Recent efforts have been made in this regard, which take into account both intersubject variability and take advantage of the power of averaging. For example, group independent component analysis (GICA) in fMRI data (Calhoun et al. 2001; Beckmann and Smith, 2005), which identifies group components and reconstructs activations at the individual level. Studies using this newer approach have shown promise when tested with simulated data (Allen et al. 2012). Regardless of the type of imaging technique and analysis employed, individual variability should not be ignored, as evidence continues to emerge that individuals may exhibit varying brain activity even within a "homogeneous" healthy group completing an identical task.

Acknowledgments

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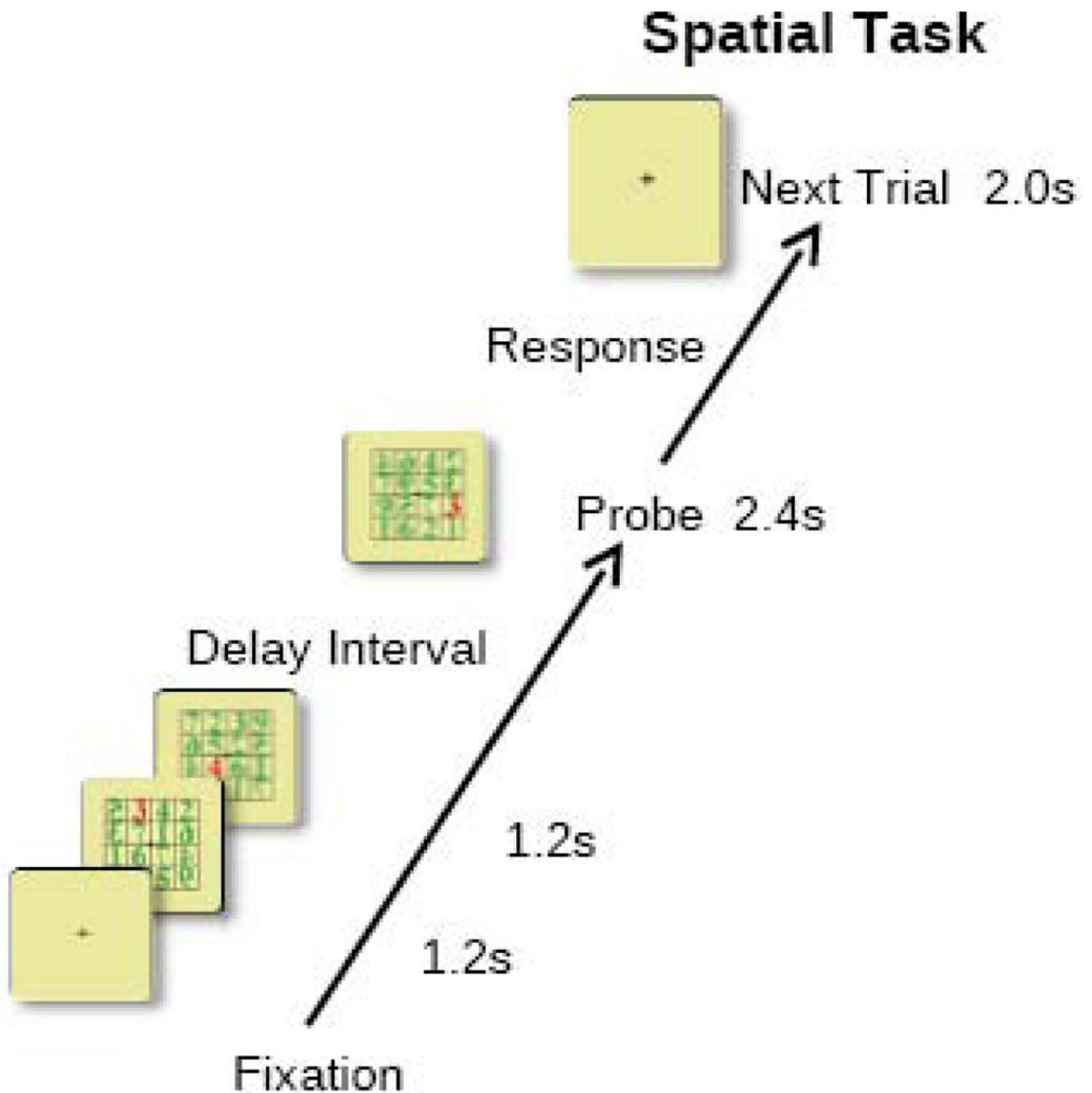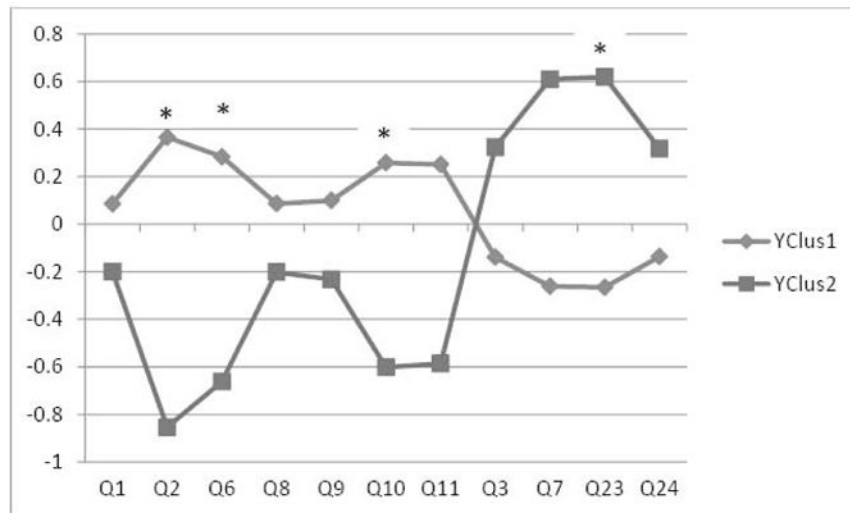
Fig. 1.
Spatial Working Memory Task. A modified Sternberg task was used to test memory performance of young healthy participants. The participants were instructed to remember the location of a red digit within an array of green digits, for 2 different arrays, presented sequentially.

Clus1: VERBAL

Q1—I thought of a word or a phrase
Q2—I created a pattern in my mind that connected the locations of the red digits
Q6—I counted over how many squares over they were and how many squares up and down
Q8—I imagined a letter on the grid that I could say to myself
Q9—I imagined the movement of chess pieces
Q10—I silently said a name of an object to myself
Q11—I could not help myself from silently saying the digit
Q3—I did not keep the digit locations in mind the way they were presented
Q7—I did not make the squares brighter or darker
Q23—I do not consider myself to have good spatial ability
Q24—I am not good at reading maps

Clus2: SPATIAL

Q1—I didn't think of a word or a phrase
Q2—I did not create a pattern in my mind that connected the locations of the red digits
Q6—I didn't count squares
Q8—I didn't imagine a letter on the grid that I could say to myself
Q9-- I didn't imagine the movement of chess pieces
Q10—I didn't silently say a name of an object to myself
Q11—I could help from saying the digit
Q3—I did keep the digit locations in mind the way they were presented
Q7—I did make the squares brighter or darker
Q23-- I do have good spatial ability
Q24-- I am good at reading maps

Fig. 2.
Cluster groups based on responses to 11 items of the questionnaire. The statements are paraphrased below, participants were asked how strongly they agreed with each statement. Highlighted items are examples that contributed to significant differences between groups.
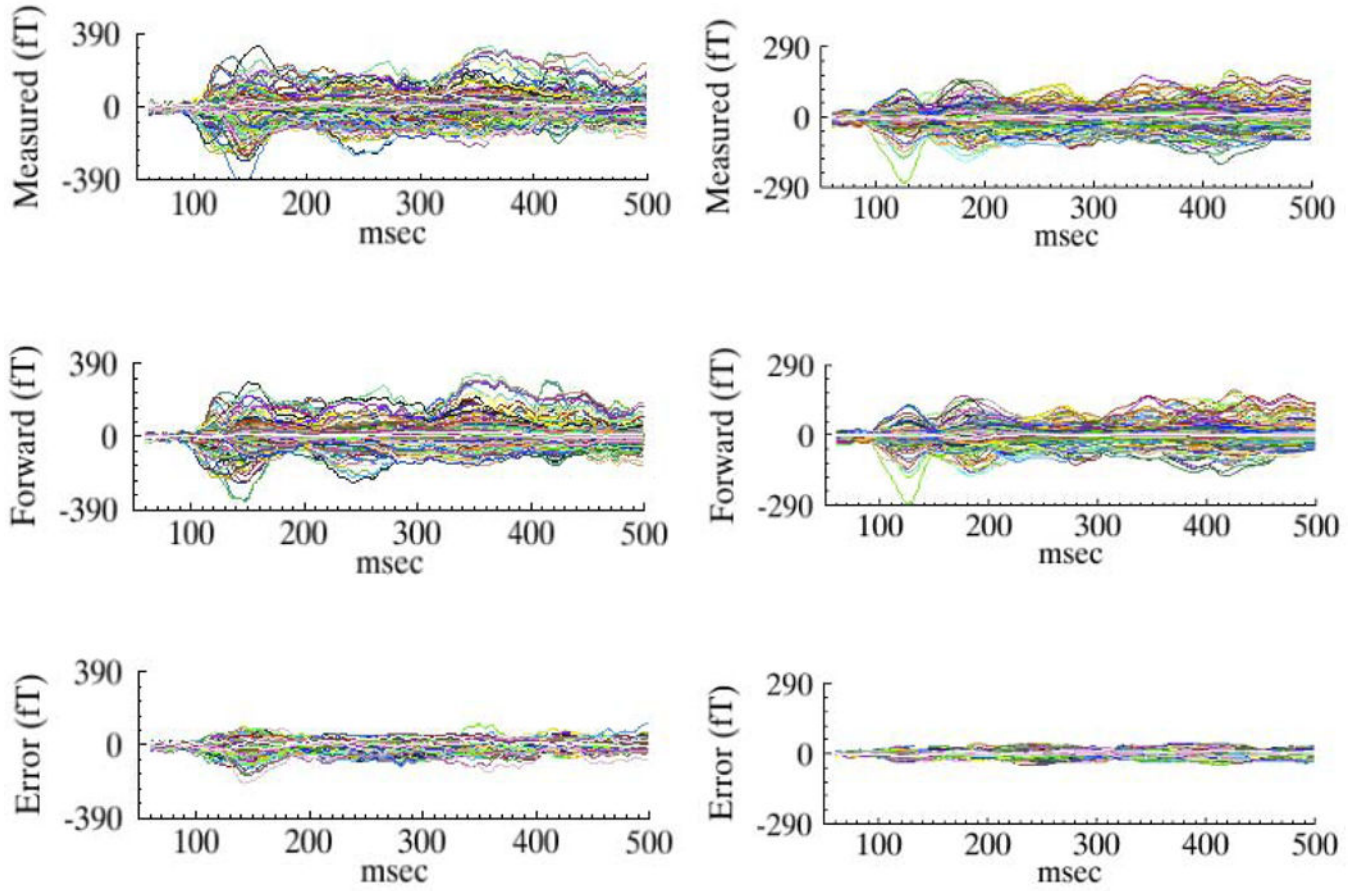
Fig. 3.
Top: Magnetic fields recorded at the sensor level (Measured). Middle: Magnetic fields reconstructed from CSST dipole solution (Forward solution). Bottom: difference between the measured and forward fields, indicating how well the model explains the original data. Shown for 2 subjects, one from the verbal group (Left) and one from the visuospatial group (Right).
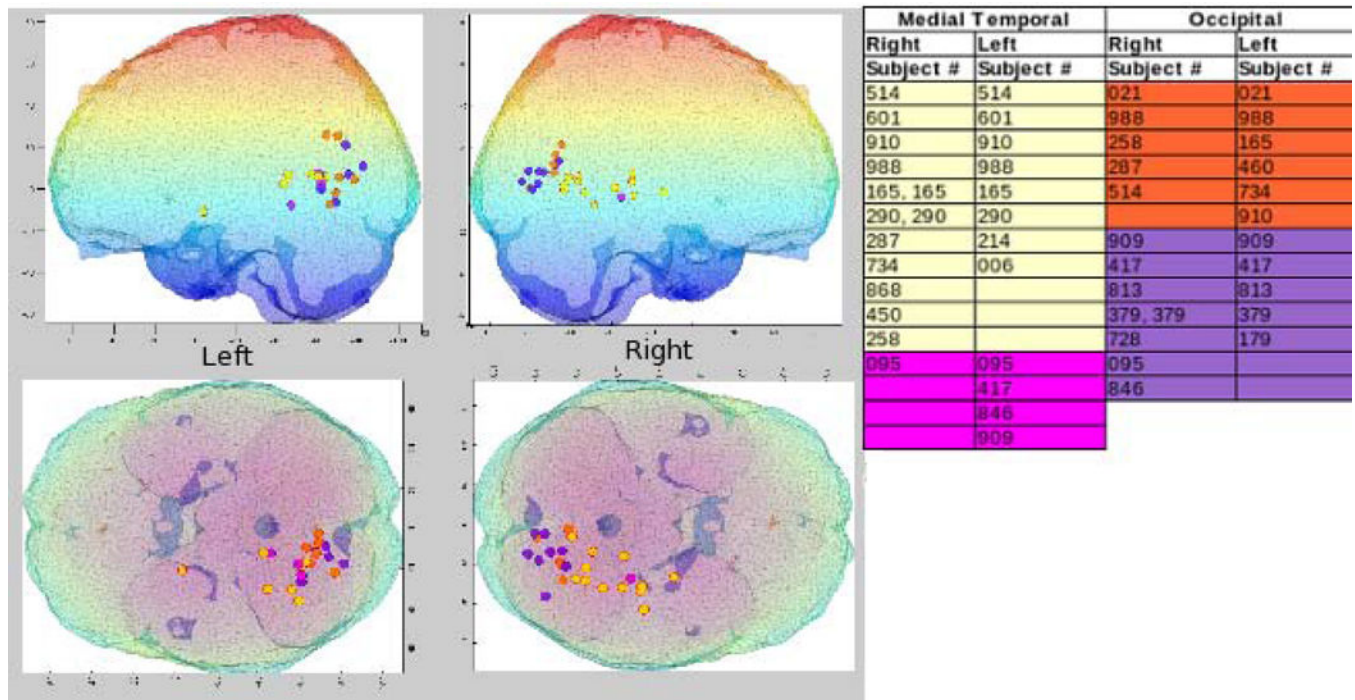
Fig. 4.
Locations of brain activity for verbal and visuospatial groups. Yellow=verbal MTL; orange = verbal OCC; pink = visuospatial MTL; purple = visuospatial OCC. Left side of mesh brain plot includes only left hemisphere sources (Top=sagittal view, Bottom=axial view, top-down). Right side of mesh brain plot includes only right hemisphere sources (Top=sagittal view, Bottom=axial view, top-down). Participants showing left/right MTL and OCC sources are included in the table at right of mesh brain plot, using the same color coding shown above. Note, color shading of the mesh brain simply reflects differing depths.
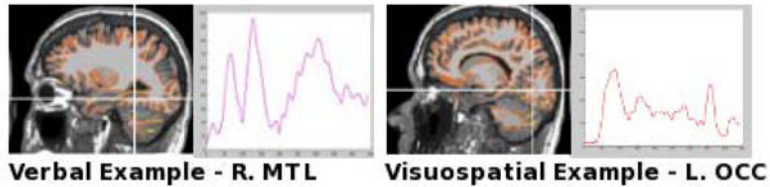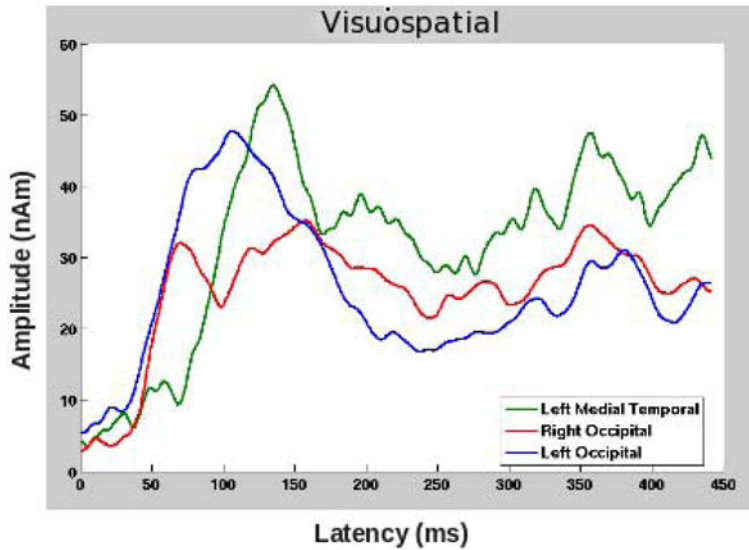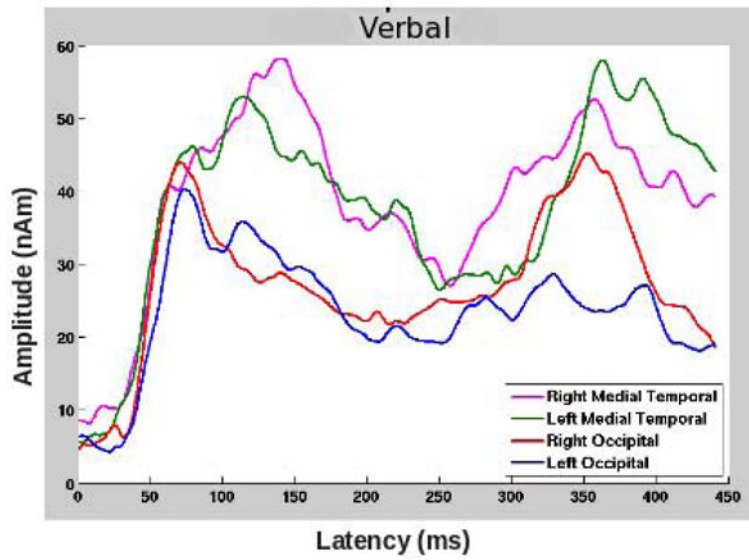
Fig. 5.
Top: Averaged timecourses across common locations for subjects who used each strategy.
Bottom: MRIs (radiological convention) displaying locations of activation (white crosshairs)
are shown for two representative individuals, one who used a verbal strategy (left) and the
other who used a visuospatial strategy (right), along with the associated timecourses for
these cortical regions. Note these are the same two individuals for which measured, modeled
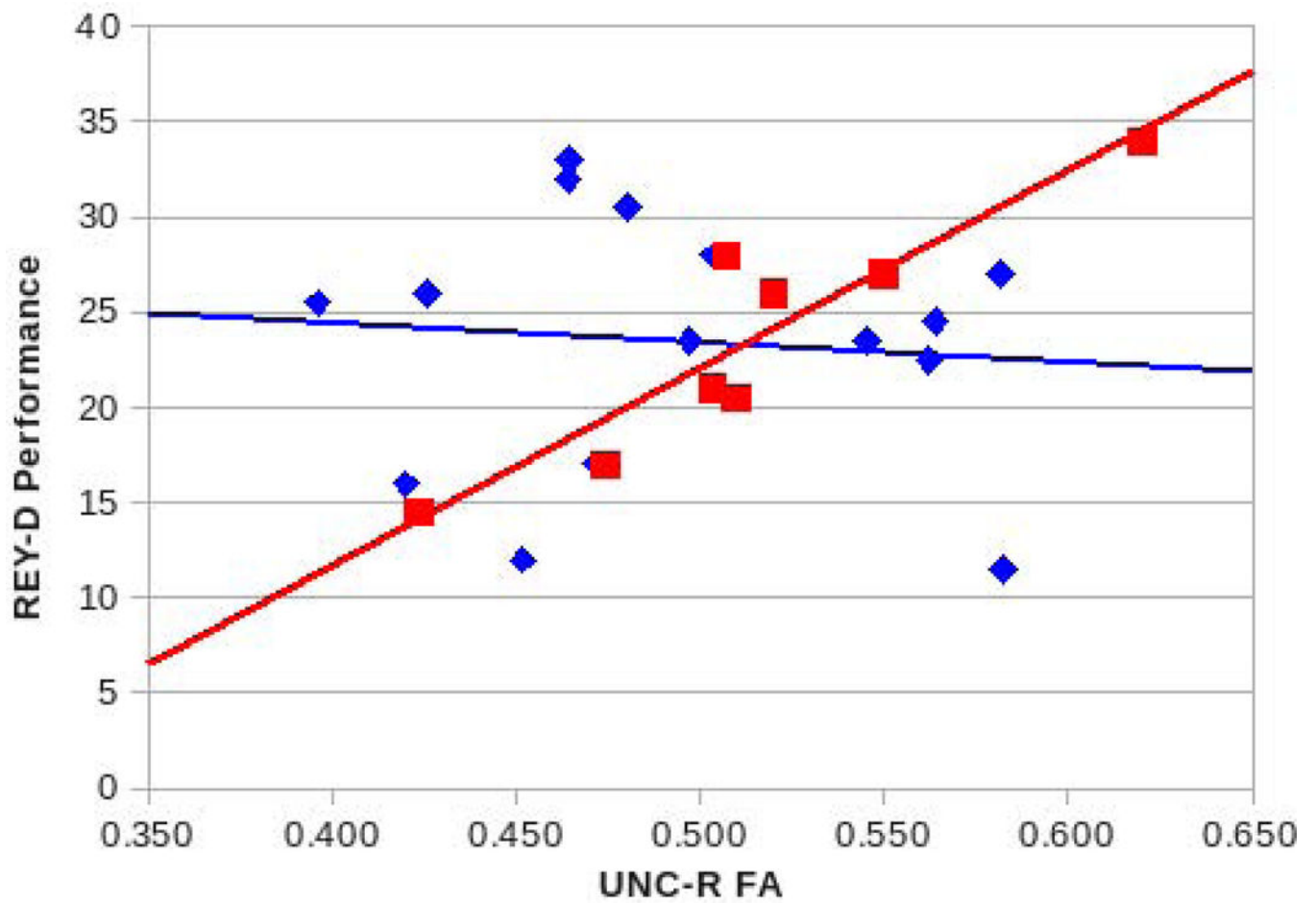and residual waveforms were shown in Fig. 3.

Fig. 6.
Correlations between FA values in UNC-R white matter tract and performance on REY-D complex figure. Red = visuospatial group, r = 0.92. Blue = verbal group, r = –0.09.

Table 1

Characteristics of the two strategy groups identified using the strategy Likert Scale. Means and Standard Deviations are shown. IQ is based on full scale score of WAIS-IV. There were no significant differences between groups on any of these variables. Trig=Triglycerides (<150 is normal); Total Chol=Total Cholesterol (<200 is desirable); HDL=High density lipoprotein (>60 is ideal); LDL=Low density lipoprotein (<100 is optimal); A1c=average blood glucose level across 3 months (<6.0 is normal); BP=Blood pressure (<120 systolic/<80 diastolic is normal). All blood tests were conducted after 12 hours fasting. Some young in both groups had lower HDL than ideal and 1 young from each group had higher systolic BP levels than normal.

Strategy Group	Age	Gender (M/F)	IQ Full WAIS	Trig mg/dL	Total Chol mg/dL	HDL mg/dL	LDL mg/dL	A1c %	BP (Sys/Dia) mmHg
Verbal	21.9 (1.9)	5/11	109.1 (9.4)	84.3 (30.4)	161.6 (31.8)	52.3 (16.2)	92.3 (27.0)	5.4 (0.4)	110.2/67.6 (11.4/8.1)
Spatial	21.4 (2.2)	5/4	104.8 (8.2)	98.6 (52.2)	154.3 (27.4)	43.3 (15.9)	91.3 (22.7)	5.5 (0.3)	114.0/68.2 (9.9/8.1)

Table 2

Colored cells denote significant correlations between white matter tracts and behavioral performance.

FDR(0.1)	Visuospatial				Verbal		
	REY	WMI	PRI		REY	WMI	PRI
PCT	0.283	0.824	0.430	PCT	0.068	0.023	0.065
BCC	0.368	0.291	0.880	BCC	−0.220	0.206	0.122
PCR-R	0.645	0.749	0.857	PCR-R	−0.044	0.391	0.264
SLF-R	0.725	0.345	0.811	SLF-R	0.070	0.507	0.388
SFO-L	0.562	0.935	0.494	SFO-L	0.043	0.069	0.094
UNC-R	0.918	0.516	0.716	UNC-R	−0.091	0.448	0.232
TAP-R	0.595	0.531	0.799	TAP-R	0.025	0.250	0.321