Behavioral/Systems/Cognitive

# A Multimodal Assessment of the Genetic Control over Working Memory

**Katherine H. Karlsgodt,[1] Peter Kochunov,[2] Anderson M. Winkler,[3,4] Angela R. Laird,[2] Laura Almasy,[5] Ravindranath Duggirala,[5] Rene L. Olvera,[2] Peter T. Fox,[2] John Blangero,[5] and David C. Glahn[3,4]**

[1]Department of Psychiatry, Cognitive Neuroscience Center, University of California Los Angeles, Los Angeles, California 90095, [2]Research Imaging Institute, University of Texas Health Science Center, San Antonio, Texas 78229, [3]Olin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, Hartford, Connecticut 06106, [4]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut 06510, and [5]Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, Texas 78227

**Working memory performance is significantly influenced by genetic factors. Here, we assessed genetic contributions to both working memory performance and neuroimaging measures focused on the network of brain regions associated with working memory by using a sample of 467 human participants from extended families. Imaging measures included diffusion tensor imaging indices in major white matter tracts thought to be associated with working memory and structural magnetic resonance imaging measures of frontal and parietal gray matter density. Analyses directly addressed whether working memory performance and neural structural integrity are influenced by common genetic factors (e.g., pleiotropy). While all cognitive measures, gray matter regions, and white matter tracts assessed were heritable, only performance on a spatial delayed response task and integrity of the superior longitudinal fasciculus (a primary fronto-parietal connection) shared genetic factors. As working memory may be a core component of other higher level processes, such as general intelligence, this finding has implications for the heritability of complex cognitive functions, as well as for our understanding of the transmission of cognitive deficits in mental and neurological disorders.**

## Introduction

Although measures of general cognitive ability ( *g* ) or intelligence are heritable (Bouchard and McGue, 1981; Devlin et al., 1997), specific genes influencing these complex cognitive processes have not been identified (Flint, 1999). One potential limitation is that intellectual capacity is not constrained to a single brain region or network (Haier et al., 2004; Jung and Haier, 2007). Therefore, decomposing this global trait into more circumscribed domains subserved by more clearly delineated brain systems could lead to novel insights into genetic influences of this complex trait. In this regard, working memory, the ability to actively hold information on-line over brief periods of time (Goldman-Rakic, 1996), may be advantageous. Although working memory is closely related to *g* (Engle et al., 1999), it is facilitated by an established network that includes the prefrontal (Jacobsen, 1936; Fuster and Alexander, 1970) and parietal lobes (Rawley and Constantinidis, 2009). Evidence that these regions show synchronized neural activity and act as a circuit (Chafee and Goldman-Rakic, 1998; Smith et al., 1998) emphasizes the importance of individual cortical regions as well as the white matter structures connecting them. A primary fronto-parietal white matter connection is the superior longitudinal fasciculus (SLF). While several white matter tracts are associated with working memory, integrity of the SLF as measured by diffusion tensor imaging (DTI) is associated with working memory performance in healthy controls (Karlsgodt et al., 2008), schizophrenia patients (Karlsgodt et al., 2008), multiple sclerosis patients (Bonzano et al., 2009; Dineen et al., 2009), patients with alcoholism (Harris et al., 2008), and across normal development (Olesen et al., 2003; Klingberg, 2006).

Although working memory performance is heritable (Ando et al., 2001; Chen et al., 2009), the biological mechanism through which working memory ability is transmitted is unknown. As working memory relies on a distributed network, genes that influence working memory may influence neuronal functioning within specific brain regions or, alternatively, the coordination of activity in these regions. The anatomical components of the working memory circuitry, such as white matter volume and microstructure (Baaré et al., 2001; Pfefferbaum et al., 2001; Hulshoff Pol et al., 2006; Chiang et al., 2009) and gray matter in frontal and parietal regions (Thompson et al., 2001), are substantially controlled by genetics. However, it is unknown whether the genetic factors that influence working memory performance also influence changes in these biological structures.

We employ a multimodal assessment of genetic influence on working memory circuitry structure and function in 467 individuals from extended families. We evaluate the genetic contribution to white matter integrity and gray matter density in regions

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Correspondence should be addressed to Dr. David C. Glahn, Olin Neuropsychiatry Research Center, Whitehall Research Building, Institute of Living, 200 Retreat Avenue, Hartford, CT 06106. E-mail: david.glahn@yale.edu.

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**Table 1. Summary of family relationships**

| Relationship | No. of pairs |
|---|---|
| Self | 462 |
| Parent-offspring | 145 |
| Siblings | 178 |
| Grandparent-grandchild | 13 |
| Avuncular | 275 |
| Half siblings | 49 |
| Double first cousins | 1 |
| Grand avuncular | 65 |
| Half avuncular | 41 |
| First cousins | 385 |
| Double first cousins, one removed | 10 |
| Half first cousins and second cousins | 1 |
| Half grand avuncular | 3 |
| First cousins, one removed | 333 |
| Half first cousins | 85 |
| Double second cousins | 28 |
| First cousins, two removed | 4 |
| Half first cousins, one removed | 12 |
| Second cousins | 163 |
| Second cousins, one removed | 45 |
| Half second cousins | 2 |

**Table 2. Working memory, gray matter, and white matter tract measures**

| Trait | Mean (SD) | Heritability | *p* value |
|---|---|---|---|
| Spatial-delayed response | 9.77 (1.4) | $0.149 \pm 0.07$ | $1.0 \times 10^{-2}$ |
| Forward digit span | 6.33 (2.1) | $0.542 \pm 0.08$ | $1.9 \times 10^{-16}$ |
| Backward digit span | 4.99 (2.0) | $0.475 \pm 0.09$ | $6.7 \times 10^{-11}$ |
| Letter number span | 7.89 (2.6) | $0.441 \pm 0.08$ | $2.5 \times 10^{-9}$ |
| Anterior limb of internal capsule | 0.529 (0.028) | $0.419 \pm 0.13$ | $2.8 \times 10^{-4}$ |
| Cingulum (cingulate bundle) | 0.439 (0.036) | $0.357 \pm 0.13$ | $9.9 \times 10^{-4}$ |
| External capsule | 0.372 (0.028) | $0.458 \pm 0.11$ | $4.5 \times 10^{-6}$ |
| Superior fronto-occipital fasciculus (SFO) | 0.522 (0.044) | $0.407 \pm 0.10$ | $4.5 \times 10^{-6}$ |
| Superior longitudinal fasciculus (SLF) | 0.433 (0.028) | $0.594 \pm 0.11$ | $1.0 \times 10^{-7}$ |
| Prefrontal gray matter density | 58.85 (6.0) | $0.619 \pm 0.13$ | $5.0 \times 10^{-7}$ |
| Parietal gray matter density | 65.85 (9.1) | $0.476 \pm 0.12$ | $6.1 \times 10^{-6}$ |

Heritability estimates for working memory, gray matter, and white matter tract measures. Means for cognitive measures are based on number correct, white matter tract means are based on average FA in the ROI (TBSS output, divided by 10,000 to yield a standard FA ratio between 0 and 1), and gray matter means on percentage of gray matter; each mean is reported with its SD. Heritability is reported as the heritability estimate, $h^2$, and SE.

associated with working memory and to working memory performance and determine whether overlapping genetic factors influence multiple traits (e.g., pleiotropy). We found that working memory performance, gray matter density, and white matter integrity were heritable, but only working memory performance and SLF integrity were affected by common genetic factors. This finding has implications for understanding working memory in both healthy controls and patients with disorders such as schizophrenia.

## Materials and Methods

*Participants.* Four hundred and sixty-seven Mexican-American individuals from 32 large extended pedigrees [average family size: 8.2 (1–38) people] participated in the "Genetics of Brain Structure and Function" study (Table 1 shows family relationships). Participants were 61% female ($n = 285$), ranged in age from 19 to 85 (mean ± SD: 47.84 ± 13.5) years, had 11.39 ± 3.5 years of education on average, and 6% were left handed. Individuals in this cohort have actively participated in genetics research for >15 years and were initially pseudorandomly selected from the community, with the constraints that they had to be of Mexican-American ancestry, be part of a large family, and live within the San Antonio region. In the current study, individuals were excluded for magnetic resonance imaging (MRI) contraindications, history of neurological illnesses, or stroke or other major neurological event. All participants provided written informed consent on forms approved by the institutional review board at the University of Texas Health Science Center San Antonio (UTHSCSA), San Antonio, TX.

*Working memory assessment.* Verbal working memory was assessed with the digit span and letter-number sequencing subtests of the WAIS-4 and with a spatial delayed response task (SDRT) (Glahn et al., 2003). The dependent measure for the forward condition of the digit-span task was the total number of digits recalled from digit strings of increasing length. The digit-span task backward condition required subjects to reorder digits held in memory and report them in reverse order. In contrast, the letter-number span required subject to reorganize letter-number strings, first reporting letters in alphabetical order, followed by numbers from lowest to highest.

During the SDRT, subjects were shown a target array of either three or five yellow circles positioned pseudorandomly around a central fixation. After a fixed delay, subjects were shown a single green circle and were required to indicate if that circle was in the same position as one of the target circles. Trial events included a 2 s target-array presentation, a 3 s delay period, and a 3 s fixed response interval (2 s intertrial interval). A central fixation was visible throughout each of the 24 trials (12 per memory set size), and memory set size was randomly ordered across the experiment. To minimize learning effects, subjects performed several example trials before beginning the test.

*Image acquisition.* Scanning was performed at the Research Imaging Center, UTHSCSA (San Antonio, TX) on a Siemens Magnetom Trio 3 T scanner with an 8-channel head coil. High-resolution (800 $\mu$m, isotropic) 3D TurboFlash T1-weighted images were acquired for each subject using a retrospective motion-corrected protocol (Kochunov et al., 2006) with the following parameters: echo time (TE) = 3.04 ms, repetition time (TR) = 2100 ms, inversion time = 785 ms, flip angle = 13. DTI data acquisition used a single-shot, single refocusing spin echo, and echo-planar imaging sequence was used to acquire diffusion-weighted data with a spatial resolution of $1.7 \times 1.7 \times 3.0$ mm. The sequence parameters were as follows: TE = 87 ms, TR = 8000 ms, field of view = 200 mm, 55 isotropically distributed diffusion weighted directions, two diffusion weighting values, $b = 0$ and 700 s/mm$^2$, and three $b = 0$ (nondiffusion-weighted) images. The number of diffusion directions, number of $b = 0$ images, and the magnitude of the $b$ values were calculated using an optimization technique that accounts for the diffusivity of the cerebral working memory and the $T_2$ relaxation times (Jones et al., 1999).

*Gray matter density image analysis.* To compare genetic contributions to gray matter density and working memory performance, high-resolution $T_1$ structural images were analyzed using a voxel-based morphometry-style approach (Ashburner and Friston, 2000; Good et al., 2001). Images were skull stripped and then aligned to a common space (MNI-152) using affine and nonlinear registration methods. The resulting images were averaged to create a study-specific template, and native-space images for each subject were then nonlinearly registered to this new template. These registered images were segmented into tissue type (gray, white, and CSF), and the resulting partial volume images underwent Jacobian modulation. To focus the analysis on the working memory circuitry, gray matter images were constrained to prefrontal and parietal regions previously identified to be associated with working memory. More specifically, bilateral prefrontal (BA 9/46) and parietal (BA 7/40) regions were identified in using a modified activation likelihood estimate (ALE) method based on data from a meta analysis of *n*-back performance by Owen and colleagues (Owen et al., 2005; Eickhoff et al., 2009), with data pooled across hemisphere to result in a single region of interest (ROI) per region. The modified ALE used here, GingerALE (Eickhoff et al., 2009), overcame a number of limitations with the original algorithm. For instance, rather than relying on subjective, user-dependent Gaussian distributions, quantitative estimates of the between-subject and between-template variability were empirically determined to more explicitly model the spatial uncertainty associated with each coordinate (a correction that also includes a weighting of each study by the number of included subjects). In addition, to anatomically constrain the tests, the permutation test was limited to regions of gray matter and modified to test for the above-chance clustering between experiments, resulting in a

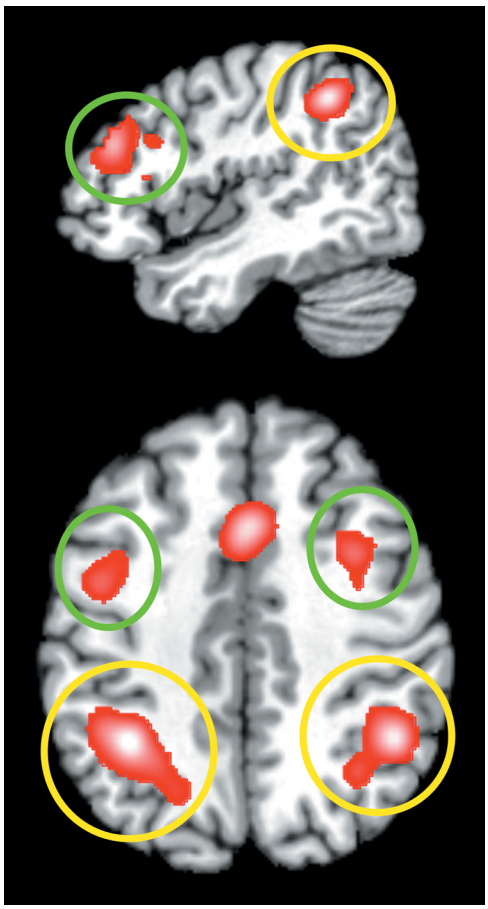

**Figure 1.** Regions of interest for gray matter density analyses: dorsolateral prefrontal and parietal lobes. Regions of activation are those identified through a meta-analysis of working memory functional MRI studies (Owen et al., 2005). The frontal and parietal regions assessed are indicated with circles.

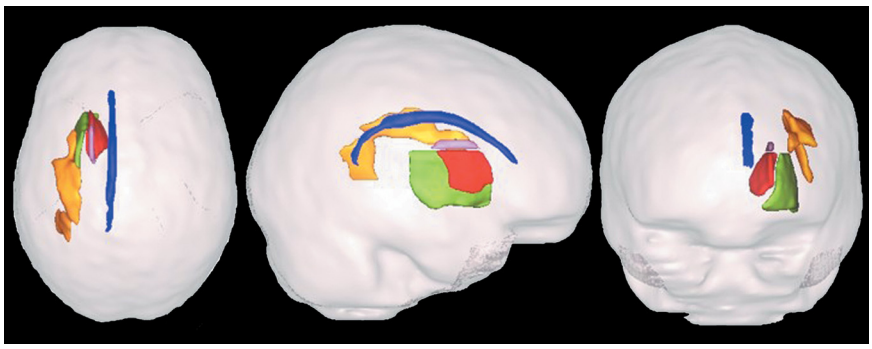

**Figure 2.** Fractional anisotropy measurements were calculated for the anterior limb of the internal capsule (red), the cingulate bundle (blue), the external capsule (green), the superior fronto-occipital fasciculus (purple), and the superior longitudinal fasciculus (yellow) using the population-based, three-dimensional, DTI, cerebral white matter tract atlas developed at Johns Hopkins University, Baltimore, MD (Wakana et al., 2004).

transition from a fixed-effects to a random-effects method of statistical inference. Finally, by progressing from an analysis based on the clustering across coordinates to the clustering across experiments, ALE results may no longer be potentially driven by a single study. The new ALE formulation was validated against the classical algorithm and experimental data and found to increase the specificity of results without losing the sensitivity of the original approach. These improvements have been implemented in the most recent version of GingerALE, which is currently available for beta testing on the BrainMap website.

*DTI image analysis.* Voxel and tract level statistics were estimated for each subject using Tract-Based Spatial Statistics (TBSS) software (Smith et al., 2006). DTI images were corrected for spatial distortions caused by eddy currents and simple head motion. After resampling each subject's fractional anisotropy (FA) image into 1 mm isotropic voxels, images were nonlinearly aligned to a minimal deformation, study-specific template. The study-specific template space was identified by warping each subject's image into all other subject images and represents the minimum deformation necessary, at the group level, to form a common space. Once in the template space, FA images were averaged to produce a group average FA image. This image was "thinned" to create a white matter skeleton representing the centers of the major tracts common to the group. Each subject's aligned FA data were projected onto the skeleton image, and the highest local FA values were assigned to the skeleton to represent the center of the tract of interest. A population-based, three-dimensional, DTI cerebral white matter tract atlas distributed with the FSL (Functional MRI of the Brain Software Library) package (Wakana et al., 2004) was used to calculate population average diffusion parameter values along the spatial course of major white matter tracts (Table 2; Fig. 1). Per-tract average values were calculated by collapsing and averaging the values along the tracts in both hemispheres resulting in one bilateral ROI for each tract. The whole-brain average diffusion values were calculated by averaging values for the entire white matter skeleton. We limited our regions of interest to the following five bilateral tracts that we hypothesized relate to regions previously associated with working memory: (1) the anterior limb of the internal capsule (ALIC), which provides fronto-thalamic connections; (2) the cingulate bundle (CB); (3) the external capsule (EC), a striatal-cortical connection; (4) the superior fronto–occipital fasciculus (SFO), connecting the frontal lobe to more posterior regions; and (5) the SLF, a frontalparietal connection.

*Quantitative genetic analyses.* All quantitative genetic analyses were conducted with Sequential Oligogenic Linkage Analysis Routines (SOLAR) (Almasy and Blangero, 1998). SOLAR employs maximum likelihood variance decomposition methods to determine the relative importance of familial and environmental influences on a measure by modeling the covariance among family members as a function of genetic proximity (kinship). To ensure that neuropsychological and neuroimaging traits conform to the assumptions of normality, an inverse normal transformation was applied. Heritability ($h^2$) represents the portion of the phenotypic variance accounted for by the total additive genetic variance ($h^2 = \sigma_g^2/\sigma_p^2$). Indices with stronger covariance between genetically more similar individuals than between genetically less similar individuals have higher heritability. Within SOLAR, this is assessed by contrasting the observed covariance matrices for a neuropsychological or neuroimaging measure with the covariance matrix predicted by kinship.

To determine whether working memory measures and white matter tracts are influenced by the same genetic factors, genetic correlation analyses were conducted. More formally, bivariate polygenic analyses were performed to estimate genetic ($\rho_g$) and environmental ($\rho_e$) correlations between working memory and white matter tract indices with the following formula: $\rho_p = \rho_g(h_1^2)^{-1/2}(h_2^2)^{-1/2} + \rho_e(1 - h_1^2)^{-1/2}(1 - h_2^2)^{-1/2}$. The significance of these correlations was tested by comparing the *ln* likelihood for two restricted models (with either $\rho_g$ or $\rho_e$ constrained to equal 0.0) against the *ln* likelihood for the model in which these parameters were estimated. A significant genetic correlation is evidence for pleiotropy, that is, a gene or set of genes influencing both phenotypes (Almasy et al., 1997). All genetic analyses were conducted with demographic covariates including age, sex, age × sex interaction, square of age, square of age × sex interaction, diagnosis status for hypertension, and diabetes. Tests were corrected for multiple comparisons at a 5% false discovery rate (FDR).

**Table 3. Genetic and environmental correlations between white matter tracts, gray matter density and working memory measures**

| | Digits forward | | Digits backward | | Letter-number | | SDRT | |
|---|---|---|---|---|---|---|---|---|
| | $\rho_g$ | $\rho_e$ | $\rho_g$ | $\rho_e$ | $\rho_g$ | $\rho_e$ | $\rho_g$ | $\rho_e$ |
| Anterior limb of internal capsule | 0.125 (0.451) | 0.004 (0.975) | 0.129 (0.504) | 0.006 (0.964) | 0.160 (0.426) | 0.039 (0.762) | 0.061 (0.843) | 0.041 (0.701) |
| Cingulum (cingulate bundle) | 0.166 (0.364) | 0.215 (0.086) | 0.018 (0.930) | 0.014 (0.914) | 0.222 (0.285) | 0.178 (0.178) | 0.458 (0.152) | 0.106 (0.310) |
| External capsule | 0.040 (0.794) | 0.032 (0.806) | 0.102 (0.562) | 0.047 (0.730) | 0.053 (0.775) | 0.037 (0.780) | 0.125 (0.646) | 0.007 (0.949) |
| Superior fronto-occipital fasciculus | 0.070 (0.667) | 0.123 (0.323) | 0.054 (0.770) | 0.038 (0.767) | 0.100 (0.593) | 0.047 (0.707) | 0.153 (0.580) | 0.091 (0.366) |
| Superior longitudinal fasciculus | 0.076 (0.595) | 0.055 (0.717) | 0.071 (0.666) | 0.094 (0.565) | 0.118 (0.490) | 0.023 (0.882) | **0.593 (0.023)** | **0.245 (0.048)** |
| Prefrontal gray matter density | 0.238 (0.103) | **−0.318 (0.039)** | 0.108 (0.515) | −0.153 (0.365) | 0.164 (0.333) | −0.072 (0.601) | 0.063 (0.808) | −0.056 (0.670) |
| Parietal gray matter density | −0.048 (0.759) | 0.134 (0.351) | 0.115 (0.532) | 0.268 (0.067) | −0.087 (0.701) | 0.052 (0.723) | −0.135 (0.659) | 0.077 (0.507) |

Genetic $\rho_g$ ( $p$ value) and environmental $\rho_e$ ( $p$ value) correlations between white matter tracts and working memory measures. Significant tests at 5% FDR are bolded.

## Results

### Heritability analysis

*Gray matter density*

Our analyses showed that density in both prefrontal and parietal ROIs was significantly heritable (false discovery rate corrected at 5%) using SOLAR (Almasy and Blangero, 1998) (see Table 2). Heritability was determined to be 0.629 (SE: 619 ± 0.13) ( $p = 5.0 \times 10^{-7}$) for the prefrontal ROI and 0.476 (±0.12) ( $p = 6.1 \times 10^{-6}$) for the parietal ROI.

*White matter tracts*

In the five bilateral white matter tracts assessed, ALIC, CB, EC, SFO, and the SLF (Fig. 2), FA measures ranged from 0.372 (±0.028) in the EC to 0.529 (±0.028) in the ALIC. All tracts were shown to be significantly heritable at 5% FDR using SOLAR. Heritability for these regions varied from $h^2 = 0.357$ [(±0.13 ( $p = 9.9 \times 10^{-4}$)] for the CB to 0.594 [(±0.11) ( $p = 1.0 \times 10^{-7}$)] for the SLF (Table 2).

*Working memory behavioral assessments*

We found all working memory measures, including digit span forward, digit span backwards, letter-number sequencing, and the SDRT to be significantly heritable at 5% FDR using SOLAR (see Table 2), ranging from $h^2 = 0.149$ [(±0.07) ( $p = 1.0 \times 10^{-2}$)] for the SDRT to 0.543 [(±0.08) ( $p = 1.9 \times 10^{-16}$)] for forward digit span. The analyses for both white matter integrity and working memory included the demographic covariates age, sex, age × sex interaction, squared age, squared age × sex interaction, as well as diagnosis status for both hypertension and diabetes. Age was significant for all neurocognitive, gray matter, and white matter measures, which is consistent with known neural changes across the lifespan and is expected in a sample with such a wide age range. In addition, the hypertension covariate was significant for the EC and SFO tracts, and sex was significant for both gray matter indices. No other covariate reached significance for the heritability or bivariate analyses.

### Bivariate analyses

Finally, having shown that structural integrity of the white matter connecting regions associated with working memory, the gray matter density in two major nodes of the working memory circuitry, as well as working memory performance itself, were indeed heritable, we next sought to determine whether common genetic factors influenced these traits. To this end, genetic and environmental correlations (bivariate polygenic analyses in SOLAR) were performed (Table 3). These analyses showed that while both individual regions and the cognitive measures were heritable, only the SLF and the SDRT showed significant levels of common genetic influences, with a genetic correlation of 0.593, $p = 0.023$.

## Discussion

We found that, while all measures in our battery of working memory assessments were heritable, as were both gray matter regions and all five white matter tracts, only spatial working memory (SDRT) performance and SLF microstructure share common genetic factors. This finding may be able to contribute to our understanding of the heritability of complex cognitive functions. It is known that working memory performance is heritable, but it has been unknown what factors contribute to variability and, thereby, potentially to heritability of this trait. While it is expected that a number of factors play a role, the present finding may inform this by suggesting one plausible biological mechanism by which variation in working memory performance may be genetically transmitted.

Imaging measures are particularly well suited for use in genetic analyses (Meyer-Lindenberg and Weinberger, 2006) as biologically based intermediate phenotypes. Such intermediate phenotypes are useful, because what is being assessed (structural brain change) is likely more proximal to factors the genes are coding for than more abstract measures, such as the level of cognitive function or indices of intelligence. Here, we see that the same genes that influence a biologically based trait also influence cognitive function. This finding supports the idea that the heritability of the cognitive traits may be mediated by the genetic influence on this underlying structural change. Our findings are consistent with previous imaging work showing that imaging indices of white matter structure (Carmelli et al., 1998; Baaré et al., 2001; Pfefferbaum et al., 2001; Peper et al., 2007; Kochunov et al., 2010) and gray matter structure (Baaré et al., 2001; Thompson et al., 2001; Peper et al., 2007) are heritable. Specifically, both frontal white matter and parietal white matter are heritable in general, as is FA in the SLF in particular (Chiang et al., 2009). In addition, previous work supports our finding that frontal lobe gray matter density is also highly heritable (Thompson et al., 2001). Furthermore, both frontal lobe gray matter thickness (Narr et al., 2007) and white matter integrity (Chiang et al., 2009) have been recently related to general intelligence measures. The present work extends this by testing a more specific cognitive function (spatial working memory) in conjunction with specific neuroanatomical structures thought to comprise the relevant circuitry (frontal and parietal gray matter and associated white matter tracts) (Jacobsen, 1936; Fuster and Alexander, 1970; Olesen et al., 2003; Klingberg, 2006; Karlsgodt et al., 2008; Rawley and Constantinidis, 2009). By using a multimodal probe of a single cognitive domain, we determined that the aspect of brain structure that is genetically related to variation in working memory performance is white matter integrity in the SLF.

Isolating factors that contribute to specific cognitive domains is important, given that basic functions like working memory

may serve as a core component that can impact several downstream, higher-level cognitive functions. Thus, the heritability of spatial working memory and its associated white matter may provide one means that can contribute to the heritability of more general complex cognitive phenotypes such as intelligent quotient (IQ) and *g*. In this light, it is of interest that while all working memory measures were heritable, the pleiotropic effects were limited to the SDRT, a highly specific experimental task designed to isolate spatial working memory maintenance. The nonexperimental neuropsychological tasks were included in the assessment, as they also probe executive function and are likely to rely to a large extent on working memory; however, they do contain complicating features. For instance, because new stimuli are serially presented, the digit span forward task includes an updating component during encoding; the digit span backwards task includes a manipulation component because the numbers must be reordered before responding, and letter number sequencing is a fairly complex task, with both task switching and manipulation components. The SDRT is an example of a more modular lower level task that can isolate specific subcomponents of other higher-level functions (ranging from working memory manipulation up to measures of intelligence). Indeed, *post hoc* tests indicate that in this sample IQ and SDRT performance were significantly correlated phenotypically ( $p = 1.274 \times 10^{-6}$). Our results show that by assessing specific simple cognitive functions for which the neural basis is well understood in combination with structural neuroimaging measures that are likely to be more proximal to the genetic effects in question, we gain the power to begin to build bridges between specific aspects of genetics, brain structure, and cognition.

While these analyses have been performed in healthy individuals, these findings have the potential to indirectly inform future research on schizophrenia, given that spatial working memory is a known endophenotype for the disorder (Cannon et al., 2000; Glahn et al., 2003, 2007) and that both gray and white matter are known to be disrupted (Cannon et al., 2002; Federspiel et al., 2006; Szeszko et al., 2007; Karlsgodt et al., 2008). In addition to evidence for a genetic influence on the gray matter in schizophrenia (Cannon et al., 2002), white matter changes seem to have a genetic component as well. For instance, expression of myelination-related genes is selectively decreased (Hakak et al., 2001). Furthermore, expression of these myelin-related genes peaks in adolescence, the period most proximal to disease onset (Harris et al., 2009). However, although patients with schizophrenia show heritable deficits in spatial working memory as well as in structural integrity in regions associated with working memory, it has been unclear whether these effects are mediated by common genetic factors or the mechanism by which such deficits might be genetically transmitted. Candidate mechanisms have included cellular signaling changes influenced by known susceptibility genes, but given the complex genetic profile of schizophrenia it is likely that there are multiple contributing factors. This work brings forward the possibility that white matter integrity may be an additional genetically transmitted factor that could potentially limit working memory function in these subjects. Understanding the roots of working memory dysfunction is of critical importance for the following reasons: (1) it is considered to be a core deficit in schizophrenia that can impact higher level cognitive processes (Silver et al., 2003); (2) it could potentially account for symptomatology such as delusions, disorganization, and thought disorder (Goldman-Rakic, 1994); and (3) it has been correlated with functional outcome (Green, 1996). Future analyses assessing this issue in patient populations will greatly inform this issue and may ultimately provide important implications for our understanding of working memory deficits in schizophrenia.

Our study is designed for and limited to finding evidence for pleiotropy. Therefore, identification of specific genes, determination of the number of genes involved, or directional conclusions about the effects are beyond the scope of this analysis. It is possible that genes are directly affecting white matter integrity and that those changes then limit cognitive function. However, it is also possible that the genes code for some aspect of cellular structure or function that impacts both the connectivity between cortical regions and the ability to employ them for working memory performance. Nonetheless, the results presented here are evidence for pleiotropy, instigating the determination of the number and identification of genes involved. Data collection in this project is ongoing, and a future goal is to identify quantitative trait loci associated with neural structure and function. Given this set of findings, the focus of such an investigation would likely be on genes that jointly influence the two traits (spatial working memory performance and SLF integrity) found to be significant here. This analysis, by collapsing the results across hemisphere in the interest of reducing the number of statistical tests, does not allow the interpretation of effects specific to each hemisphere. *Post hoc* tests did indicate that FA of the SLFs in the right and left hemispheres were each independently heritable ($H^2r = 0.5776$, $p = 3.8369 \times 10^{-8}$ and $H^2r = 0.5205$, $p = 0.0000048$, respectively); however, the relationship of SLF integrity and working memory performance only achieved trend-level significance for right ( $p = 0.06$) and left ( $p = 0.08$) hemispheres, likely due to the decreased variance that occurs when collapsing across measures. Such a laterality-based comparison may be the subject of future analyses focusing more specifically on the SLF. In addition, our sample was constrained to individuals from large extended families and, as such, may slightly limit the generalizability of the results.

Overall, this work may elucidate one potential mechanism by which differences in working memory performance may be genetically transmitted. This has implications for both our understanding of the heritability of more complex cognitive functions in healthy subjects, as well as how specific deficits may be transmitted in disorders such as schizophrenia.

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