Published in final edited form as:
J Neurosci. 2010 June 16; 30(24): 8197–8202. doi:10.1523/JNEUROSCI.0359-10.2010.

A Multimodal Assessment of the Genetic Control over Working Memory

KH Karlsgodt[1], **P Kochunov**[2], **AM Winkler**[3,4], **AR Laird**[2], **L Almasy**[5], **R Duggirala**[5], **RL Olvera**[2], **PT Fox**[2], **J Blangero**[5], and **DC Glahn**[3,4]

[1] Department of Psychiatry, Cognitive Neuroscience Center, University of California Los Angeles, Los Angeles, CA, USA

[2] Research Imaging Institute, University of Texas Health Science Center San Antonio, San Antonio, TX, USA

[3] Olin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, Hartford, CT, USA

[4] Department of Psychiatry, Yale University School of Medicine, New Haven, CT USA

[5] Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX, USA

Abstract

Working memory performance is significantly influenced by genetic factors. Here, we assessed genetic contributions to both working memory performance and to neuroimaging measures focused on the network of brain regions associated with working memory, using a sample of 467 human participants from extended families. Imaging measures included diffusion tensor imaging (DTI) indices in major white matter tracts thought to be associated with working memory and structural MRI 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 frontoparietal 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.

Keywords

white matter; diffusion tensor imaging; DTI; spatial working memory; heritability; genetic correlation

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

Corresponding Author: David C Glahn Ph.D., Olin Neuropsychiatry Research Center, Whitehall Research Building, Institute of Living, 200 Retreat Ave, Hartford, CT 06106, Office (860) 545-7298, Fax (860) 545-7797, david.glahn@yale.edu.

Financial disclosure: None of the authors have financial interests to disclose.

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 including 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 frontoparietal 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), 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 (Baare 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 multi-modal 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 associated with working memory, and to working memory performance, and determine if 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.

Methods and Materials

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 (see Table 1 for family relationships). Participants were 61% female (n=285), ranging in age from 19 to 85 (mean±standard deviation: 47.84±13.5) years, had 11.39±3.5 years of education on average and were 6% left handed. Individuals in this cohort have actively participated in genetics research for over 15 years and were initially pseudo-randomly 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 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).

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 3 or 5 yellow circles positioned pseudo-randomly 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-second target-array presentation, a 3-second delay period and a 3-second fixed response interval (2-second inter-trial 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, on a Siemens Magnetom Trio 3 T scanner with an 8-channel head coil. High-resolution (800 μm, 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: TE/TR/TI = 3.04/2100/785 ms, flip angle = 13. DTI data acquisition used a single-shot single refocusing spin-echo, echo-planar imaging sequence was used to acquire diffusion-weighted data with a spatial resolution of 1.7×1.7×3.0mm. The sequence parameters were: TE/TR=87/8000ms, FOV=200mm, 55 isotropically distributed diffusion weighted directions, two diffusion weighting values, b=0 and 700 s/mm^2 and three b=0 (non-diffusion-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 T2 relaxation times (Jones et al., 1999).

Gray Matter Density Image Analysis

In order to compare genetic contributions to gray matter density and working memory performance, high-resolution T1 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 non-linearly 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. In order 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 ROI per region. The modified ALE employed 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 in order 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 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 no longer may potentially be 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 software (TBSS)(Smith et al., 2006). DTI images were corrected for spatial distortions due to eddy currents and simple head motion. After resampling each subject's 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 was 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, 3D, DTI cerebral working memory tract atlas distributed with the FSL package (Wakana et al., 2004) was used to calculate population average diffusion parameter values along the spatial course of major working memory tracts (Table 2, Figure 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 five bilateral tracts we hypothesized to relate to regions previously associated with working memory: the anterior limb of the internal capsule (ALIC) which provides frontothalamic connections, the cingulate bundle (CB), the external capsule (EC) a striatal-cortical connection, the superior fronto-occipital fasciculus (SFO) connecting the frontal lobe to more posterior regions, and the superior longitudinal fasciculus (SLF) a frontal-parietal 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 ($h^2 = \sigma^2_g/\sigma^2_p$). 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 if 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 (ρ_g) and environmental (ρ_e) correlations between working memory and white-matter tract indices with the following formula: $\rho_p=\rho_g(h^2_1)^{-1/2}h^2_2)^{-1/2}+\rho_e(1-h^2_1)^{-1/2}(1-h^2_1)^{-1/2}$. The significance of these correlations was tested by comparing the *ln* likelihood for two restricted models (with either ρ_g or ρ_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 a gene or set of genes influences 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% FDR.

Results

Heritability Analysis

Gray Matter Density—Our analyses showed that density in both pre-frontal 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 (standard error: 619±0.13) ($p = 5.0\times10^{-7}$) for the prefrontal ROI, and 0.476(± 0.12) ($p = 6.1\times10^{-6}$) for the parietal ROI.

White Matter Tracts—In the five bilateral white matter tracts assessed: ALIC, CB, EC, SFO, and the SLF (see Figure 2) FA measures ranged from .372 (±.028) in the EC to .529 (±.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($p = 9.9\times10^{-4}$)) for the CB to 0.594 ((± 0.11) ($p = 1.0\times10^{-7}$) for the SLF (see 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 from h^2= 0.149((± 0.07) ($p = 1.0\times10^{-02}$) for the SDRT to 0.543((± 0.08) ($p= 1.9\times10^{-16}$) 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, 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 (see Table 3). These analyses showed that while both individual regions and the cognitive measures were heritable, only the SLF and the SDRT that 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 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 are more abstract measures, such as 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 (Kochunov, 2010; Carmelli, 1998; Baare, 2001; Pfefferbaum, 2001; Peper, 2007) and grey matter structure (Thompson, 2001; Peper, 2007; Baare, 2001) are heritable. Specifically, both frontal 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). Further, 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 employing 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 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 non-experimental 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 as 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 sub-components of other higher-level functions (ranging from working memory manipulation up to measures of intelligence). And indeed, post-hoc tests indicate that in this sample IQ and SDRT performance were significantly phenotypically correlated ($p= 1.274 \cdot 10^{-6}$). 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; Glahn et al., 2007) and both gray and white matter are known to be disrupted (i.e. (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; it is considered to be a core deficit in schizophrenia that can impact higher level cognitive processes (Silver et al., 2003), could potentially account for symptomatology such as delusions, disorganization, and thought disorder (Goldman-Rakic, 1994), and 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 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 (QTLs) 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 SLF in the right and left hemispheres were each independently heritable ($H2r = 0.5776$; $p = 3.8369e\text{-}08$ and $H2r = 0.5205$; $p = 0.0000048$, respectively), however the relationship of SLF integrity and working memory performance only achieved trend-level significance for right ($p = 0.06$) and left ($p=.08$) 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.

Acknowledgments

Financial support for this study was provided by NIMH grants MH0708143 (PI: DC Glahn), MH078111 (PI: J Blangero), MH083824 (PI: DC Glahn) MH074457 (PI: PT Fox) and NIBIB grant EB006395 (PI P. Kochunov). SOLAR is supported by NIMH grant MH59490 (J Blangero).

References

Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet 1998;62:1198–1211. [PubMed: 9545414]

Almasy L, Dyer TD, Blangero J. Bivariate quantitative trait linkage analysis: pleiotropy versus coincident linkages. Genet Epidemiol 1997;14:953–958. [PubMed: 9433606]

Ando J, Ono Y, Wright MJ. Genetic structure of spatial and verbal working memory. Behav Genet 2001;31:615–624. [PubMed: 11838538]

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000;11:805–821. [PubMed: 10860804]

Baare WF, Hulshoff Pol HE, Boomsma DI, Posthuma D, de Geus EJ, Schnack HG, van Haren NE, van Oel CJ, Kahn RS. Quantitative genetic modeling of variation in human brain morphology. Cereb Cortex 2001;11:816–824. [PubMed: 11532887]

Bonzano L, Pardini M, Mancardi GL, Pizzorno M, Roccatagliata L. Structural connectivity influences brain activation during PVSAT in Multiple Sclerosis. Neuroimage 2009;44:9–15. [PubMed: 18790063]

Bouchard TJ Jr. McGue M. Familial studies of intelligence: a review. Science 1981;212:1055–1059. [PubMed: 7195071]

Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, Finkelstein J, Hietanen M, Kaprio J, Koskenvuo M. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. Am J Hum Genet 2000;67:369–382. [PubMed: 10880296]

Cannon TD, Thompson PM, van Erp TG, Toga AW, Poutanen VP, Huttunen M, Lonnqvist J, Standerskjold-Nordenstam CG, Narr KL, Khaledy M, Zoumalan CI, Dail R, Kaprio J. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. Proc Natl Acad Sci U S A 2002;99:3228–3233. [PubMed: 11867725]

Chafee MV, Goldman-Rakic PS. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J Neurophysiol 1998;79:2919–2940. [PubMed: 9636098]

Chen LS, Rice TK, Thompson PA, Barch DM, Csernansky JG. Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia. Schizophr Res 2009;111:159–166. [PubMed: 19398304]

Chiang MC, Barysheva M, Shattuck DW, Lee AD, Madsen SK, Avedissian C, Klunder AD, Toga AW, McMahon KL, de Zubicaray GI, Wright MJ, Srivastava A, Balov N, Thompson PM. Genetics of brain fiber architecture and intellectual performance. J Neurosci 2009;29:2212–2224. [PubMed: 19228974]

Devlin B, Daniels M, Roeder K. The heritability of IQ. Nature 1997;388:468–471. [PubMed: 9242404]

Dineen RA, Vilisaar J, Hlinka J, Bradshaw CM, Morgan PS, Constantinescu CS, Auer DP. Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. Brain 2009;132:239–249. [PubMed: 18953055]

Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 2009;30:2907–2926. [PubMed: 19172646]

Engle RW, Tuholski SW, Laughlin JE, Conway AR. Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. J Exp Psychol Gen 1999;128:309–331. [PubMed: 10513398]

Federspiel A, Begre S, Kiefer C, Schroth G, Strik WK, Dierks T. Alterations of white matter connectivity in first episode schizophrenia. Neurobiol Dis 2006;22:702–709. [PubMed: 16624566]

Flint J. The genetic basis of cognition. Brain 1999;122(Pt 11):2015–2032. [PubMed: 10545388]

Fuster JM, Alexander GE. Delayed response deficit by cryogenic depression of frontal cortex. Brain Res 1970;20:85–90. [PubMed: 4986430]

Glahn DC, Therman S, Manninen M, Huttunen M, Kaprio J, Lonnqvist J, Cannon TD. Spatial working memory as an endophenotype for schizophrenia. Biol Psychiatry 2003;53:624–626. [PubMed: 12679242]

Glahn DC, Almasy L, Blangero J, Burk GM, Estrada J, Peralta JM, Meyenberg N, Castro MP, Barrett J, Nicolini H, Raventos H, Escamilla MA. Adjudicating neurocognitive endophenotypes for schizophrenia. Am J Med Genet B Neuropsychiatr Genet 2007;144B:242–249. [PubMed: 17034022]

Goldman-Rakic PS. Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 1994;6:348–357. [PubMed: 7841806]

Goldman-Rakic PS. Regional and cellular fractionation of working memory. Proc Natl Acad Sci U S A 1996;93:13473–13480. [PubMed: 8942959]

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21–36. [PubMed: 11525331]

Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321–330. [PubMed: 8610818]

Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT. Structural brain variation and general intelligence. Neuroimage 2004;23:425–433. [PubMed: 15325390]

Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, Haroutunian V, Fienberg AA. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci U S A 2001;98:4746–4751. [PubMed: 11296301]

Harris GJ, Jaffin SK, Hodge SM, Kennedy D, Caviness VS, Marinkovic K, Papadimitriou GM, Makris N, Oscar-Berman M. Frontal white matter and cingulum diffusion tensor imaging deficits in alcoholism. Alcohol Clin Exp Res 2008;32:1001–1013. [PubMed: 18422840]

Harris LW, Lockstone HE, Khaitovich P, Weickert CS, Webster MJ, Bahn S. Gene expression in the prefrontal cortex during adolescence: implications for the onset of schizophrenia. BMC Med Genomics 2009;2:28. [PubMed: 19457239]

Hulshoff Pol HE, Schnack HG, Posthuma D, Mandl RC, Baare WF, van Oel C, van Haren NE, Collins DL, Evans AC, Amunts K, Burgel U, Zilles K, de Geus E, Boomsma DI, Kahn RS. Genetic contributions to human brain morphology and intelligence. J Neurosci 2006;26:10235–10242. [PubMed: 17021179]

Jacobsen CF. Studies of cerbral function in primates:I. The functions of the frontal association areas in monkeys. Comparative Psychology Monographs 1936;13:1–60.

Jones DK, Simmons A, Williams SC, Horsfield MA. Non-invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magn Reson Med 1999;42:37–41. [PubMed: 10398948]

Jung RE, Haier RJ. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. Behav Brain Sci 2007;30:135–154. discussion 154-187. [PubMed: 17655784]

Karlsgodt KH, van Erp TG, Poldrack RA, Bearden CE, Nuechterlein KH, Cannon TD. Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. Biol Psychiatry 2008;63:512–518. [PubMed: 17720147]

Klingberg T. Development of a superior frontal-intraparietal network for visuo-spatial working memory. Neuropsychologia. 2006

Kochunov P, Lancaster JL, Glahn DC, Purdy D, Laird AR, Gao F, Fox P. Retrospective motion correction protocol for high-resolution anatomical MRI. Hum Brain Mapp 2006;27:957–962. [PubMed: 16628607]

Meyer-Lindenberg A, Weinberger D. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nature Reviews Neuroscience 2006;7:808–827.

Narr KL, Woods RP, Thompson PM, Szeszko P, Robinson D, Dimtcheva T, Gurbani M, Toga AW, Bilder RM. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cereb Cortex 2007;17:2163–2171. [PubMed: 17118969]

Olesen PJ, Nagy Z, Westerberg H, Klingberg T. Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. Brain Res Cogn Brain Res 2003;18:48–57. [PubMed: 14659496]

Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 2005;25:46–59. [PubMed: 15846822]

Pfefferbaum A, Sullivan EV, Carmelli D. Genetic regulation of regional microstructure of the corpus callosum in late life. Neuroreport 2001;12:1677–1681. [PubMed: 11409738]

Rawley JB, Constantinidis C. Neural correlates of learning and working memory in the primate posterior parietal cortex. Neurobiol Learn Mem 2009;91:129–138. [PubMed: 19116173]

Silver H, Feldman P, Bilker W, Gur RC. Working memory deficit as a core neuropsychological dysfunction in schizophrenia. Am J Psychiatry 2003;160:1809–1816. [PubMed: 14514495]

Smith EE, Jonides J, Marshuetz C, Koeppe RA. Components of verbal working memory: evidence from neuroimaging. Proc Natl Acad Sci U S A 1998;95:876–882. [PubMed: 9448254]

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487–1505. [PubMed: 16624579]

Szeszko PR, Robinson DG, Ashtari M, Vogel J, Betensky J, Sevy S, Ardekani BA, Lencz T, Malhotra AK, McCormack J, Miller R, Lim KO, Gunduz-Bruce H, Kane JM, Bilder RM. Clinical and Neuropsychological Correlates of White Matter Abnormalities in Recent Onset Schizophrenia. Neuropsychopharmacology. 2007

Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen M, Lonnqvist J, Standertskjold-Nordenstam CG, Kaprio J, Khaledy M, Dail R, Zoumalan CI, Toga AW. Genetic influences on brain structure. Nat Neurosci 2001;4:1253–1258. [PubMed: 11694885]

Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology 2004;230:77–87. [PubMed: 14645885]

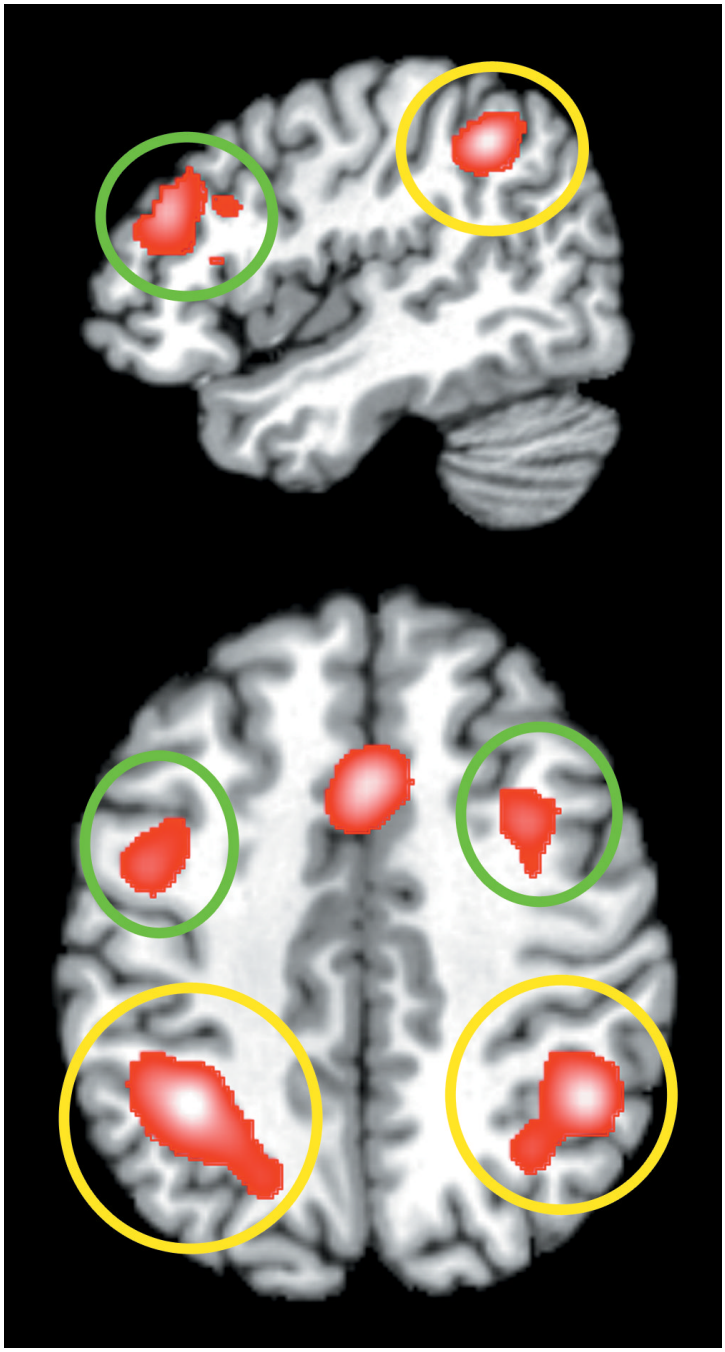

Figure 1.
Regions of interest for grey matter density analyses: dorsolateral prefrontal and parietal lobes. Regions of activation are those identified through a meta-analysis of working memory fMRI studies (Owen et al, 2005). The frontal and parietal regions assessed are indicated with circles.

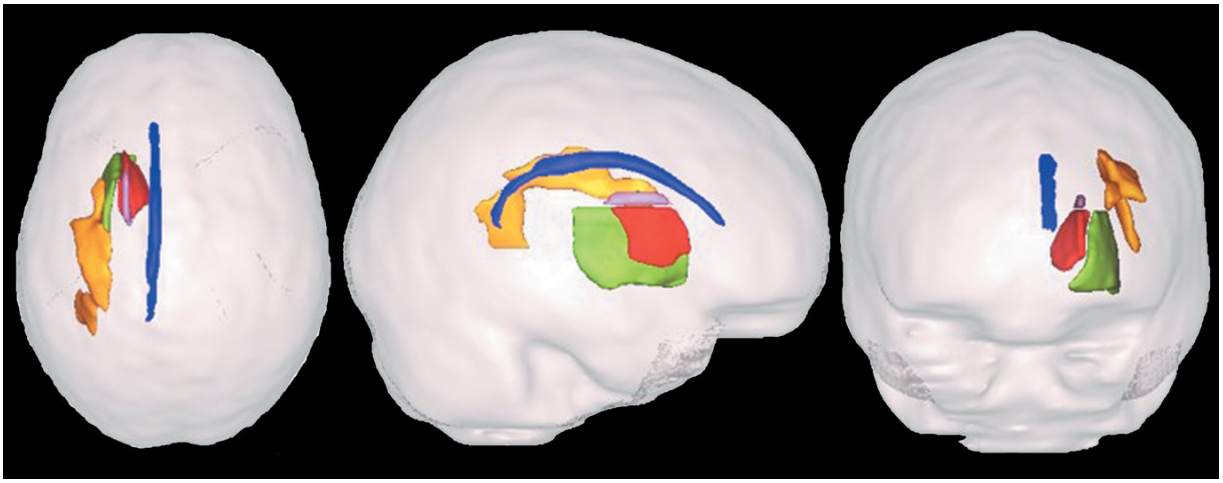

Figure 2.
Fractional anistropy measurements were calculated for the anterior limb of the internal capsule (red), the cingulate bundle (blue), the external capsule (green), the superior fronto-occipital fasciculus (purple), and the superior longitudinal fasciculus (yellow) using the population-based, 3D, DTI, cerebral working memory tract atlas, developed in John Hopkins University (Wakana, et al., 2004)

Table 1

Summary of Family Relationships

RELATIONSHIP	NUMBER OF PAIRS
Self	462
Parent-offspring	145
Siblings	178
Grandparent-grandchild	13
Avuncular	275
Half siblings	49
Double 1st cousins	1
Grand avuncular	65
Half avuncular	41
1st cousins	385
Double 1st cousins, 1 removed	10
Half 1st cousins & 2nd cousins	1
Half grand avuncular	3
1st cousins, 1 removed	333
Half 1st cousins	85
Double 2nd cousins	28
1st cousins, 2 removed	4
Half 1st cousins, 1 removed	12
2nd cousins	163
2nd cousins, 1 removed	45
Half 2nd 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 ± (0.07)	1.0×10^{-02}
Forward Digit Span	6.33 (2.1)	0.542 ± (0.08)	1.9×10^{-16}
Backward Digit Span	4.99 (2.0)	0.475 ± (0.09)	6.7×10^{-11}
Letter Number Span	7.89 (2.6)	0.441 ± (0.08)	2.5×10^{-09}
Anterior Limb of Internal Capsule (ALIC)	.529 (.028)	0.419 ± (0.13)	2.8×10^{-04}
Cingulum (cingulate bundle) (CB)	.439 (.036)	0.357 ± (0.13)	9.9×10^{-04}
External Capsule (EC)	.372 (.028)	0.458 ± (0.11)	4.5×10^{-06}
Superior Fronto-Occipital Fasciculus (SFO)	.522 (.044)	0.407 ± (0.10)	4.5×10^{-06}
Superior Longitudinal Fasciculus (SLF)	.433 (.028)	0.594 ± (0.11)	1.0×10^{-07}
Prefrontal Gray Matter Density	58.85 (6.0)	0.619 ± (0.13)	5.0×10^{-07}
Parietal Gray Matter Density	65.85 (9.1)	0.476 ± (0.12)	6.1×10^{-06}

Table 3

Genetic and Environmental Correlations between White Matter Tracts, Gray Matter Density and Working Memory Measures

	DIGITS FORWARD		DIGITS BACKWARD		LETTER-NUMBER		SDRT	
	ρ_g	ρ_e	ρ_g	ρ_e	ρ_g	ρ_e	ρ_g	ρ_e
Anterior Limb of Internal Capsule (ALIC)	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; CB)	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 (EC)	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 (SFO)	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 (SLF)	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)