Published in final edited form as:

Schizophr Res. 2008 August ; 103(1-3): 62–70. doi:10.1016/j.schres.2008.05.012.

Neuroanatomical Substrates of Foresight in Schizophrenia

Shaun M. Eack^{1,2}, Manish M. George³, Konasale M. R. Prasad¹, and Matcheri S. Keshavan^{1,45}

¹Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

²School of Social Work, University of Pittsburgh

³School of Medicine, Imperial College London

⁴Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine

Abstract

The ability to think of the long-term consequences of one's behavior and use this information to guide present and future actions, commonly referred to as foresight, is a key higher-order cognitive ability that may be deficient among persons with schizophrenia and substantially limit the degree to which such individuals experience a functional recovery from the disease. This research investigated the neuroanatomical basis of foresight in schizophrenia, in order to identify potential brain regions that may underly impaired foresightfulness among this population. Participants in the early course of schizophrenia or schizoaffective disorder ($N = 50$) were assessed using structural magnetic resonance imaging and clinician-rated measures of foresight and psychopathology. Voxel-based morphometry was used to examine the relationship between foresight and regional gray matter volume in the ventromedial prefrontal, orbitofrontal and cingulate cortices. Significant positive associations were observed between foresight and gray matter volume density in the right orbitofrontal, ventromedial prefrontal, and posterior cingulate cortices, as well as the left ventromedial prefrontal and anterior cingulate cortices, after correcting for multiple comparisons. These relationships persisted after adjusting for age, gender, illness duration, and psychopathology. Better foresight was most strongly associated with increased gray matter in the right orbitofrontal/ventromedial prefrontal cortex, suggesting that reductions in gray matter volume in this region may be associated with impaired foresight in schizophrenia. Implications and directions for future research are discussed.

1. Introduction

Schizophrenia is a chronic and disabling mental disorder that is frequently characterized by an array of social and cognitive deficits. Over the past several decades research has underscored the conceptualization of schizophrenia as a disorder, in part of basic and social cognition (Keefe & Fenton, 2007). Individuals with the disease have been repeatedly shown to exhibit a wide array of deficits in cognition (Heinrichs & Zakzanis, 1998; Penn et al., 1997), many of which have been linked to poor functional outcomes (Couture et al., 2006; Green et al., 2000). Unfortunately, while the investigation of cognitive dysfunction in schizophrenia has been extensive, most studies have focused on single cognitive domains, such as working

⁵Address correspondence to Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

memory, and tended to ignore higher-order cognitive abilities that rely on an integration of basic cognitive processes.

One particular area of inquiry that has been largely overlooked is the examination of impairments in the higher-order cognitive ability of *foresight* among this population. Foresight has been a key domain in cognitive research among a range of clinical populations (e.g., Atance & O'Neill, 2001; Lilienfeld et al., 1996; Petry et al., 1998; Wallace, 1956), and broadly refers to the ability to think of the long-term consequences of one's behavior and use this information to guide present and future actions. A review of the interdisciplinary, and at times disparate, literature surrounding foresight and future thinking suggests a multidimensional model of foresightfulness consisting of future orientation/time perspective, time horizon, delay of gratification, and consideration of future consequences. Future orientation refers to the degree to which a person generally thinks about the future (e.g., Lens, 1986; Lewin, 1951); time horizon concerns how far in the future someone thinks (e.g., Loewenstein & Elster, 1992); delay of gratification concerns the postponement of smaller, immediate for larger, delayed rewards (e.g., Metcalfe & Mischel, 1999); and consideration of future consequences is the degree to which a person thinks about the potential consequences of his/her behavior (e.g., Strathman, Gleicher, Boninger, & Edwards, 1994). Each of these dimensions of foresight is supported by its own empirical literature, and have been shown in several studies to be psychometrically distinguishable from each other and such related constructs as impulsivity (Fellows & Farah, 2005; Lane, Cherek, Rhoades, Pietras, & Tcheremissine, 2003; Strathman, Gleicher, Boninger, & Edwards, 1994; Zimbardo & Boyd, 1999), although some do conceptualize cognitive impulsivity as largely a deficit in these domains of foresightfulness and executive control (e.g., Barratt & Patton, 1983). Further, all of these abilities and foresight in general have been posited to have a substantial neurobiological basis and theorized to rely on the integration of a number of basic cognitive domains, particularly episodic memory and executive function systems (Suddendorf & Corballis, in press).

Recently we introduced this concept of foresight as a promising area of cognitive investigation in schizophrenia research. In a longitudinal study of foresight among early course patients with schizophrenia, we demonstrated that such individuals tended to exhibit low levels of foresight across the course of a 1 year study period. Furthermore, level of foresightfulness at baseline was shown to be a significant cross-sectional and longitudinal predictor of functional outcome, above and beyond negative symptomatology and deficits in neurocognitive function (Eack & Keshavan, 2008), signifying the clinical relevance of this area of investigation. In this research, we now turn to the question of whether impaired foresight in schizophrenia is a unique biobehavioral marker of the disease, by examining the association of impaired foresight with abnormalities in underlying neuroanatomy.

Several studies among other clinical populations have found abnormalities in ventromedial prefrontal and parietal cortical regions to be associated with impairments in foresightfulness. Perhaps the most famous case study linking brain anomalies to impaired foresight is that of Phineas Gage. After sustaining significant damage to the medial frontal lobes (Damasio et al., 1994), Gage was noted as becoming "impatient of restraint or advice when it conflicts with his desires" and "devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible" (Harlow, 1868), demonstrating marked impairments in delay of gratification and future planning. More recent case control studies on individuals with brain lesions have continued to implicate the medial frontal lobes in foresightfulness. Specifically, several studies have shown that lesions in the ventromedial prefrontal (vmPFC) and orbitofrontal (OFC) cortices produce profound deficits in foresight with regard to both time perspective (Fellows & Farah, 2005) and sensitivity to future consequences (Bechara et al., 1994). In addition, a minority of functional neuroimaging studies among healthy and clinical samples has also implicated the cingulate cortex in foresightfulness,

by demonstrating significant posterior cingulate cortex (PCC) activation during delay of gratification tasks (Wittmann et al., 2007).

Neuroimaging studies of constructs related to foresight, such as impulsivity and choice anticipation, among individuals with schizophrenia have also been illustrative in implicating the orbitofrontal and cingulate cortices. In one study with schizophrenia patients, Quintana and colleagues (2004) found reduced anterior cingulate cortex (ACC) activation during a choice anticipation task, which the investigators speculated may be generally associated with poor foresight. In a diffusion tensor imaging study, Hoptman and colleagues (2002) found preliminary evidence for an association between reduced fractional anisotropy and impulsiveness among individuals with schizophrenia. The findings of these investigators were confirmed in a subsequent investigation that indicated an association between self-reported impulsiveness and reduced fractional anisotropy in white matter tracts of the ACC and inferior frontal regions among a sample of males with schizophrenia (Hoptman et al., 2004).

Taken together, these findings point to the functional relevance of the vmPFC, OFC, and different components of the cingulate cortex in supporting foresightfulness. This is not surprising, given that all of these regions have been implicated in numerous decision-making paradigms, where the anticipation of future consequences is central (Glimcher & Rustichini, 2004; McClure et al., 2004). Therefore, it seems reasonable to assume that if persons with schizophrenia experience impairments in foresight, such a deficit may be associated with neuropathology in these regions. Although previous schizophrenia research has consistently shown both abnormal structure and function within many of these areas (Honea et al., 2005; Shenton et al., 2001), to date no study has directly examined how such abnormalities are related to foresight impairments among this population. This research takes the first step in addressing this question by examining the relationship between individual differences in foresight and brain morphology among persons with early course schizophrenia.

2. Method

2.1. Participants

Participants in this research included 50 individuals in the early course of schizophrenia ($n = 33$) or schizoaffective disorder ($n = 17$) participating in a randomized-controlled trial of Cognitive Enhancement Therapy (Hogarty & Greenwald, 2006). All participants were interviewed using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2002) to confirm psychiatric diagnostic status. Eligible participants included those experiencing their first psychotic symptom within the past 10 years, patients with an $IQ \geq 80$, patients who had not been abusing substances within 2 months prior to study enrollment, and those showing significant social and cognitive disability as assessed by a structured interview (Hogarty et al., 2004). Participants were predominantly Caucasian ($n = 34$) and young, with an average age of 25.95 ($SD = 6.46$) years and an average illness length of 3.18 ($SD = 2.59$) years. Approximately two-thirds were male ($n = 33$) and most had completed some college ($n = 37$), although the majority of participants were not employed ($n = 35$). A total of 59 participants were recruited to participate in this research, although only 50 had complete clinical and imaging data at baseline for analysis.

2.2. Measures

Foresight was measured using 2 clinician-rated global assessment items included as part of a larger battery developed to assess social cognition in schizophrenia (Hogarty et al., 2004). Foresight items included, "Inability to assess long-term consequences (good and bad) of behavior; difficulty forming long range plans" and "Could see the future outcome of behavior; took a long view." Both items were rated on a 5-point anchored scale, with lower scores

indicating poorer foresight, by clinicians intimately involved in the patient's treatment and carefully trained in administration of these measures by the original authors of the instruments. Items were then averaged to compute a single foresight rating. Previous research with these measures has indicated that the larger battery of social cognition from which these foresight items were derived possess adequate levels of inter-rater reliability (Hogarty et al., 2004), and that these particular measures of foresight contain adequate levels of divergent construct validity (Eack & Keshavan, 2008). In addition, to adjust for the potential confounding effects of symptomatology on brain morphology and foresight, psychopathology data were also collected by the same clinician raters using total scores from the Brief Psychiatric Rating Scale (Overall & Gorham, 1962).

2.3. Image Acquisition and Processing

Structural magnetic resonance images (MRI) were acquired using a 3-T Signa whole body scanner and head coil (GE Medical Systems, Milwaukee, WI). Whole brain volume was acquired in 124 1.5mm-thick contiguous coronal slices with spoiled gradient recalled acquisition in steady state pulse sequence (TE = 5ms, TR = 25ms, acquisition matrix = 256×192 , FOV = 24cm). Structural images were checked manually for motion and quality by independent, masters-level research associates. Images were normalized to standard MNI space and segmented using the unified segmentation algorithm (Ashburner & Friston, 2005) in SPM5 based on the default adult MNI template provided by the software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). The segmented images were then smoothed using a 12mm Gaussian kernel. Radio frequency inhomogeneity artifacts were corrected during image post-processing using a bias correction algorithm built into the segmentation procedure. Region of interest (ROI) analyses used image masks provided by the Wake Forest University PickAtlas toolbox for SPM5 (Maldjian et al., 2003), with regional definitions outlined by Tzourio-Mazoyer et al. (2002).

2.4. Procedures

Participants were recruited from Western Psychiatric Institute and Clinic in Pittsburgh and several nearby community clinics. Upon recruitment, participants were randomized to a trial of Cognitive Enhancement Therapy or an active control, and assessed yearly using a battery containing the aforementioned measures of foresight and structural MRI. This study makes use of baseline data collected from this clinical trial, and no significant baseline differences were found between treatment groups with regard to demographic characteristics, foresight, or brain morphology, after adjusting for multiple comparisons. All participants gave written, informed consent prior to participation in this research, and the study protocol was approved and reviewed annually by the University of Pittsburgh Institutional Review Board.

2.5. Data Analysis

Whole brain and ROI voxel-based morphometry (Ashburner & Friston, 2000; VBM) analyses implementing a series of multiple regression models were used to examine the association between gray matter volume density and foresight, after adjusting for the effects of age, gender, illness duration, and psychopathology on brain morphology. ROI analyses were conducted first to examine the associations between foresight and gray matter volume density in the vmPFC, OFC, ACC, and PCC. Post-hoc analyses of the moderating effects of gender on these relations were also examined. An FDR corrected type I error rate of .05, after small volume correction on regions showing voxel-level significance at $p \leq .001$ was used as the threshold for detecting significant voxel-wise associations. No minimum number of voxel clusters was required. Subsequently, an exploratory whole brain VBM analysis was conducted to identify potential regions outside our *a priori* defined regions of interest that might show some association with foresight. Again, the moderating effects of gender on the association between

foresight and brain morphology was explored. In order to adjust for inflations the type I error rate at the whole-brain level of analysis, a Monte Carlo simulation was conducted with AlphaSim (Ward, 2000) to provide appropriate voxel-extent thresholds for voxels showing significance at $p \leq .001$, which provided more of a balance between type I and II errors than the FDR method. Due to the exploratory nature of these analyses, the corrected type I error rate was set to .10 and in accordance with our simulations the corresponding uncorrected type I error rate and voxel extent size thresholds were set to .001 and 118, respectively.

3. Results

3.1. Are Medial Frontal and Cingulate Gray Matter Volumes Related to Foresight in Schizophrenia?

We began our investigation of the neurobiological correlates of foresight in schizophrenia by first conducting a ROI VBM analysis to examine the relationship between foresight and gray matter volume density in the OFC, vmPFC, ACC and PCC, after adjusting for age, gender, illness duration, and psychopathology. On average, patients in this research were rated as having moderate to severe impairments in foresight by study clinicians ($M = 2.21$, $SD = .51$, range = 1–3), and we expected those individuals with greater impairments in foresight to also demonstrate reduced volumetric densities in the aforementioned medial frontal and cingulate regions.

As can be seen in Table 1, both bilateral vmPFC and the right OFC gray matter volume densities showed significant positive associations with foresight, such that smaller gray matter volume concentrations were associated with poorer foresight. In addition, smaller right PCC and left ACC gray matter volume densities were also significantly associated with poorer foresight. The range of effect sizes for all significant relationships is presented in Figure 1, which shows voxel-level η^2 weights from the regression models predicting gray matter volume density from foresight. As can be seen in this figure, all of these regions displayed a maximum of medium-sized ($\eta^2 > .35$) associations with foresight, after adjusting for age, gender, illness duration, and psychopathology. Further, all of these associations remained statistically significant after adjusting for multiple comparisons (Table 1). No significant interactions between foresight and gender were found for any of these morphometric associations.

It is important to note that the largest and strongest cluster of voxel relations with foresight centered around the right vmPFC and OFC. To investigate the veracity of this relationship, we extracted gray matter volumes from all significant voxels (uncorrected $p < .01$) in this voxel cluster using modulated images, and performed a regression analysis predicting these volumes from foresight, after adjusting for intracranial volume, age, gender, illness duration, and psychopathology. As can be seen in Figure 2, right vmPFC and OFC volumes continued to serve as a significant predictor of foresight, lending some confirmatory support to the results from our VBM analysis.

3.2. What Other Brain Regions Are Associated With Foresight in Schizophrenia?

Having found evidence pointing to a relationship between foresight and brain morphology in our hypothesized regions of interest, particularly the right vmPFC and OFC, we then conducted an exploratory whole brain VBM analysis to examine the relationship between foresight and gray matter morphology in other regions of the brain. As can be seen in Table 2, the largest and most intense cluster of voxel relations continued to lie within the right vmPFC and OFC, as they did in our ROI analysis, and no significant additional positive associations were found that met our voxel extent and type I error rate thresholds. However, several significant gender by foresight interactions were present, indicating that poorer foresight was more strongly associated with decreased gray matter volume density in the left OFC and angular gyrus, as

well as the right dorsolateral prefrontal cortex in males compared to females. Evidence of significant relations in these regions were not seen at the whole-brain or ROI level in the overall sample, and upon inspection of within-gender analyses, relations between foresight and gray matter density volume in these areas appeared to be reserved only for males.

4. Discussion

Research on cognition in schizophrenia has largely focused on domain-specific cognitive abilities (e.g., working memory), and tended to ignore higher-order and meta-cognitive functions that rely on an integration of basic cognitive processes. Such higher-order cognitive processes may be particularly important to functional outcomes, and therefore warrant investigation (Koren et al., 2006). Foresight, or the ability to think of the long-term consequences of one's behavior and use this information to guide present and future actions, is a key higher-order cognitive ability that may be impaired in schizophrenia due to abnormalities in underlying neuroanatomy, and may explain a range of functional disabilities in the disease (Eack & Keshavan, 2008). While previous research among brain-injured populations has provided substantial evidence for the neural basis of foresight, frequently implicating the medial frontal and cingulate cortices (e.g., Fellows & Farah, 2005; Wittmann et al., 2007), and persons with schizophrenia have been shown to have functional and structural abnormalities within these regions (Honea et al., 2005; Shenton et al., 2001), no study has examined the link between such abnormalities and foresight impairment among this population. This study takes the first step in examining the neural basis of impaired foresight among persons with schizophrenia, by using voxel-based morphometry to examine the association between gray matter volume density in the medial frontal and cingulate cortices and foresight among a sample of early course patients.

The primary results of this research indicate the presence of significant positive associations between foresight and gray matter volume densities in the bilateral vmPFC, right OFC and PCC, as well as the left ACC, suggesting an association between poor foresight in schizophrenia and reduced gray matter volume in select regions of the medial frontal and cingulate cortices. Exploratory whole brain also revealed several interactions with gender, pointing to the potential additional impact of reductions in gray matter volume in the left orbitofrontal cortex, angular gyrus, and right dorsolateral prefrontal cortex in subverting foresightfulness among male patients. Further, these results could not be attributed to individual differences in psychopathology or illness duration. Consistent with previous research with other populations (e.g., Fellows & Farah, 2005), these findings largely highlight the role of the vmPFC, OFC, and cingulate cortex in supporting a capacity for foresight and increasingly point to its aberrance among persons with schizophrenia. When coupled with our previous findings indicating that foresight is a unique longitudinal contributor to functional outcome among this population, these results suggest that impaired foresight may represent a key biobehavioral marker of the disease and its functional course. In turn, the remediation of foresight and broader functional outcome in schizophrenia may depend on interventions that act on the neuronal systems associated with the medial frontal and cingulate cortices.

Firm conclusions regarding the significance of foresight impairments in schizophrenia and their neurobiological correlates, however, are admittedly premature as this exploratory investigation contains a number of important limitations. First, while our global, clinician-rated measurements of foresight provide an accurate and reliable description of the overall level of foresightfulness a person displays (Eack & Keshavan, 2008; Hogarty et al., 2004), such measures are less adept in separating the different dimensions of foresight (e.g., future orientation, delay of gratification), which may not necessarily be equally associated with gray matter volume in the medial frontal and cingulate cortices. Future research needs to employ more specific measures of foresight that adequately assess the range of dimensions of this

concept, in order to clearly identify the neurobiological substrates most closely associated with different components of foresight. The development of performance-based assessments could be particularly promising, as such measures would allow for the assessment of not only the propensity, but also the capacity to use foresight, and allow for a broader range of neurobiological investigations (e.g., fMRI, DTI).

Second, it is important to remember that this study was not a controlled examination of foresight impairment in schizophrenia, but rather consisted of an investigation of how individual differences in foresight *within* schizophrenia patients are associated with alterations in brain morphology. A medial frontal neurobiologic deficit in schizophrenia seems clear, given that consistent evidence has pointed to the altered morphology and function of these regions in this population (Honea et al., 2005; Shenton et al., 2001). Less clear is the degree to which foresight deficits are present in and specific to schizophrenia, as no controlled studies of foresight among this population have been conducted. However, our initial longitudinal investigation of foresight in schizophrenia did show profound deficits in this domain throughout the course of a 1 year study period, which were significantly predictive of functional outcome (Eack & Keshavan, 2008). This study extends these findings by taking the initial step in showing that these impairments in foresight are related to the medial frontal deficit commonly described in schizophrenia. Nonetheless, controlled investigations are clearly needed not only to identify the magnitude and specificity of foresight impairments among this population, but also to clarify the degree to which reduced gray matter volume in the medial frontal and cingulate cortices adequately distinguishes foresight ability between persons with schizophrenia and healthy individuals.

Finally, future research could benefit from employing larger and more diverse samples of persons with schizophrenia to verify the generalizability of these findings. While the modest sample size employed in this research allowed for the detection of moderate-sized relationships between foresight and gray matter volume in the medial frontal and cingulate cortices, additional associations of less magnitude may also exist that this research was not able to detect. Further, given that individuals in this research were selected based on systematic criteria for inclusion in a trial of Cognitive Enhancement Therapy, they may not resemble the more general population of people who suffer from schizophrenia. In particular, our sample was quite young, and may exhibit a restricted range of foresight scores that could obscure relationship estimates. As such, it will be important for future research to verify these results using larger and more general samples of persons with schizophrenia.

References

- Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* 2005;26(3):839–851. [PubMed: 15955494]
- Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *Neuroimage* 2000;11(6):805–821. [PubMed: 10860804]
- Atance CM, O'Neill DK. Episodic future thinking. *Trends in Cognitive Sciences* 2001;5(12):533–539. [PubMed: 11728911]
- Barratt, ES.; Patton, JH. Impulsivity: Cognitive, behavioral, and psychophysiological correlates. In: Zuckerman, M., editor. *The biological bases of sensation seeking, impulsivity, and anxiety*. Hillsdale, NJ: Erlbaum; 1983. p. 77-116.
- Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50(1–3):7–15. [PubMed: 8039375]
- Couture SM, Penn DL, Roberts DL. The Functional Significance of Social Cognition in Schizophrenia: A Review. *Schizophr. Bull* 2006 32;;S44–S63. [PubMed: 16916889]
- Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science* 1994;264(5162):1102–1105. [PubMed: 8178168]

- Eack SM, Keshavan MS. Foresight in schizophrenia: A potentially unique and relevant factor to functional disability. *Psychiatr. Serv* 2008;59(3):256–260. [PubMed: 18308905]
- Fellows LK, Farah MJ. Dissociable elements of human foresight: a role for the ventromedial frontal lobes in framing the future, but not in discounting future rewards. *Neuropsychologia* 2005;43(8):1214–1221. [PubMed: 15817179]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview For DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
- Glimcher PW, Rustichini A. Neuroeconomics: The Consilience of Brain and Decision. *Science* 2004;306(5695):447–452. [PubMed: 15486291]
- Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the right stuff. *Schizophr. Bull* 2000;26(1):119–136. [PubMed: 10755673]
- Harlow JM. Recovery from the passage of an iron bar through the head. *Publication of the Massachusetts Medical Society* 1868;2:327–347.
- Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* 1998;12(3):426–445. [PubMed: 9673998]
- Hogarty, GE.; Greenwald, DP. University of Pittsburgh Medical Center: Authors. Cognitive Enhancement Therapy: The Training Manual. 2006. Available through www.CognitiveEnhancementTherapy.com.
- Hogarty GE, Flesher S, Ulrich R, Carter M, Greenwald D, Pogue-Geile M, et al. Cognitive enhancement therapy for schizophrenia. Effects of a 2-year randomized trial on cognition and behavior. *Arch. Gen. Psychiatry* 2004;61(9):866–876. [PubMed: 15351765]
- Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am. J. Psychiatry* 2005;162(12):2233–2245. [PubMed: 16330585]
- Hoptman MJ, Ardekani BA, Butler PD, Nierenberg J, Javitt DC, Lim KO. DTI and impulsivity in schizophrenia: a first voxelwise correlational analysis. *Neuroreport* 2004;15(16):2467–2470. [PubMed: 15538176]
- Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. *Biol. Psychiatry* 2002;52(1):9–14. [PubMed: 12079725]
- Keefe R, S E, Fenton WS. How Should DSM-V Criteria for Schizophrenia Include Cognitive Impairment? *Schizophr. Bull* 2007;33(4):912–920. [PubMed: 17567627]
- Koren D, Seidman LJ, Goldsmith M, Harvey PD. Real-World Cognitive--and Metacognitive--Dysfunction in Schizophrenia: A New Approach for Measuring (and Remediating) More Right Stuff. *Schizophr. Bull* 2006;32(2):310–326. [PubMed: 16397202]
- Lane SD, Cherek DR, Rhoades HM, Pietras CJ, Tcheremissine OV. Relationships Among Laboratory and Psychometric Measures of Impulsivity: Implications in Substance Abuse and Dependence. *Addictive Disorders and Their Treatment* 2003;2(2):33–40.
- Lens, W. Future time perspective: A cognitive--motivational concept. In: Brown, DR.; Veroff, J., editors. *Frontiers of motivational psychology*. New York: Springer; 1986. p. 173–190.
- Lewin, K. *Field theory in the social sciences: Selected theoretical papers*. New York: Harper; 1951.
- Lilienfeld SO, Hess T, Rowland C. Psychopathic personality traits and temporal perspective: A test of the short time horizon hypothesis. *Journal of Psychopathology and Behavioral Assessment* 1996;18(3):285–303.
- Loewenstein, G.; Elster, J. *Choice over time*. New York: Russell Sage Foundation Publications; 1992.
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fmri data sets. *NeuroImage* 2003;19(3):1233–1239. [PubMed: 12880848]
- McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate Neural Systems Value Immediate and Delayed Monetary Rewards. *Science* 2004;306(5695):503–507. [PubMed: 15486304]
- Metcalfe J, Mischel W. A hot/cool-system analysis of delay of gratification: Dynamics of willpower. *Psychol. Rev* 1999;106(1):3–19. [PubMed: 10197361]

- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol. Rep* 1962;10:799–812.
- Penn DL, Corrigan PW, Bentall RP, Racenstein J, Newman L. Social cognition in schizophrenia. *Psychol. Bull* 1997;121(1):114–132. [PubMed: 9000894]
- Petry NM, Bickel WK, Arnett M. Shortened time horizons and insensitivity to future consequences in heroin addicts. *Addiction* 1998;93(5):729–738. [PubMed: 9692271]
- Quintana J, Wong T, Ortiz-Portillo E, Marder SR, Mazziotta JC. Anterior cingulate dysfunction during choice anticipation in schizophrenia. *Psychiatry Research: Neuroimaging* 2004;132(2):117–130.
- Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr. Res* 2001;49(1–2):1–52. [PubMed: 11343862]
- Strathman A, Gleicher F, Boninger DS, Edwards CS. The consideration of future consequences: Weighing immediate and distant outcomes of behavior. *J. Pers. Soc. Psychol* 1994;66(4):742–752.
- Suddendorf T, Corballis M. The evolution of foresight: What is mental time travel and is it unique to humans. *Behavioral and Brain Sciences*. in press
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 2002;15(1):273–289. [PubMed: 11771995]
- Wallace W. Future time perspective in schizophrenia. *J. Abnorm. Psychol* 1956;52(2):240–245. [PubMed: 13306440]
- Ward, DB. Simultaneous inference for fMRI data. Milwaukee, WI: Author; 2000.
- Wittmann M, Leland DS, Paulus MP. Time and decision making: differential contribution of the posterior insular cortex and the striatum during a delay discounting task. *Exp. Brain Res* 2007;179(4):643–653. [PubMed: 17216152]
- Zimbardo PG, Boyd JN. Putting time in perspective: A valid, reliable individual-differences metric. *J. Pers. Soc. Psychol* 1999;77(6):1271–1288.

Figure 1.
Beta Contrast Images of the Association Between Gray Matter Volume Density and Foresight.

Figure 2. Relationship Between Foresight and Right Orbitofrontal/Ventromedial Prefrontal Cortex Gray Matter Volume.

Region of Interest Voxel-Based Morphometric Analyses Examining the Associations Between Medial Frontal and Cingulate Cortex Gray Matter Volume Densities and Foresight (N = 50).

MINI Coordinates (x, y, z)	Cluster Size	Location	BA	z	p	pFDR	Direction
44, 40, 2	128	Right ventromedial prefrontal/ orbitofrontal cortex	10/47	4.17	< .001	.024	positive
8, -50, 28	39	Right posterior cingulate	31	3.82	< .001	.024	positive
-14, 42, 14	39	Left anterior cingulate	10/32	3.39	< .001	.031	positive
-44, 34, 8	28	Left ventromedial prefrontal cortex	46	3.41	< .001	.031	positive

BA = Brodmann's Area

Whole Brain Voxel-Based Morphometric Analyses Examining the Association Between Gray Matter Volume Density and Foresight (N = 50).

MNI Coordinates (x, y, z)	Cluster Size	Location	BA	z	p	Direction
42, 40, 2	225	Right ventromedial prefrontal/ orbitofrontal cortex	10/47	4.18	< .001	positive
-20, 48, -12	132	Foresight X Gender Interactions Left orbitofrontal cortex Right dorsolateral prefrontal cortex Left angular gyrus	11	4.13	< .001	Male > Female
12, 48, 34	127		9	4.59	< .001	Male > Female
-48, -58, -28	120		39	4.31	< .001	Male > Female

BA = Brodmann's Area