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Neuroanatomical substrates of foresight in schizophrenia

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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 underlie 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.

Keywords: Schizophrenia; Cognition; Foresight; Social cognition; Neuroimaging

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 and Fenton, 2007). Individuals with the disease have been repeatedly shown to exhibit a wide array of deficits in cognition (Heinrichs and 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

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investigation of cognitive dysfunction in schizophrenia has been extensive, most studies have focused on single cognitive domains, such as working 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 and 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 and Elster, 1992); delay of gratification concerns the postponement of smaller, immediate for larger, delayed rewards (e.g., Metcalfe and 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, and 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 and Farah, 2005; Lane et al., 2003; Strathman et al., 1994; Zimbardo and Boyd, 1999), although some do conceptualize cognitive impulsivity as largely a deficit in these domains of foresightfulness and executive control (e.g., Barratt and 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 and Corballis, 2007).

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, the 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 and 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 and 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 et al. (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 et al. (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