The Influence of Encoding Strategy on Episodic Memory and Cortical Activity in Schizophrenia

Aaron Bonner-Jackson, Kristen Haut, John G. Csernansky, and Deanna M. Barch

Background: *Recent work suggests that episodic memory deficits in schizophrenia may be related to disturbances of encoding or retrieval. Schizophrenia patients appear to benefit from instruction in episodic memory strategies. We tested the hypothesis that providing effective encoding strategies to schizophrenia patients enhances encoding-related brain activity and recognition performance.*

Methods: *Seventeen schizophrenia patients and 26 healthy comparison subjects underwent functional magnetic resonance imaging scans while performing incidental encoding tasks of words and faces. Subjects were required to make either deep (abstract/concrete) or shallow (alphabetization) judgments for words and deep (gender) judgments for faces, followed by subsequent recognition tests.*

Results: *Schizophrenia and comparison subjects recognized significantly more words encoded deeply than shallowly, activated regions in inferior frontal cortex (Brodmann area 45/47) typically associated with deep and successful encoding of words, and showed greater left frontal activation for the processing of words compared with faces. However, during deep encoding and material-specific processing (words vs. faces), participants with schizophrenia activated regions not activated by control subjects, including several in prefrontal cortex.*

Conclusions: *Our findings suggest that a deficit in use of effective strategies influences episodic memory performance in schizophrenia and that abnormalities in functional brain activation persist even when such strategies are applied.*

Key Words: Episodic memory, fMRI, schizophrenia, strategy

Memory impairment in schizophrenia is a hallmark cognitive feature of the illness (Aleman et al 1999; for a review, see Kuperberg and Heckers 2000). One possible explanation for this impairment is that individuals with schizophrenia fail to use effective memory strategies. Strategic deficits have been reported in individuals with schizophrenia during tests of episodic memory (Brebion et al 1997; Gold et al 1992; Iddon et al 1998), as well as altered patterns of brain activation during both encoding and retrieval. Individuals with schizophrenia can benefit behaviorally when provided with effective encoding strategies, but the influence of such strategies on encoding-related brain activation has not been examined.

Episodic memory, the memory of unique events (Tulving 1983), is impaired in people with schizophrenia (Achim and Lepage 2003; Clare et al 1993; Danion et al 2001; Gold et al 1992; Rushe et al 1999; Toulopoulou et al 2003), but the mechanisms that lead to such impairment are unknown. One such mechanism may be that individuals with schizophrenia fail to generate effective mnemonic strategies when encoding and retrieving verbal information (Iddon et al 1998; Koh 1978; McClain 1983) or to encode verbal stimuli properly (Larsen and Fromholt 1976; Traupmann 1980). Interestingly, when provided with strategies that encourage deep semantic processing of stimuli, people with schizophrenia show improved subsequent memory (Koh and Peterson 1978; Ragland et al 2003), although it is not fully normalized.

The hypothesis that people with schizophrenia have deficits in the use of effective strategies in memory tasks is consistent with the presence of deficits in the function of the prefrontal cortex (PFC), particularly the dorsolateral PFC (Barch et al 2002; Fletcher et al 1998; Hofer et al 2003; Weinberger et al 1986). Patients with frontal lobe damage demonstrate planning difficulties (Shallice 1982) and show impaired use of organizational strategies (Gershberg and Shimamura 1995). Furthermore, impaired frontal lobe activity has been associated with impaired task performance in episodic memory paradigms (Barch et al 2002; Hazlett et al 2000; Heckers et al 1998; Ragland et al 2004; Weiss et al 2003). Deficits in frontal lobe activation in schizophrenia remain, however, even when memory performance is similar to control subjects (Crespo-Facorro et al 1999). These findings suggest that the application of memory strategies by people with schizophrenia are subserved by prefrontal regions (Nohara et al 2000; Ragland et al 2001, 2004), although altered hippocampal activity may also be involved (e.g., Barch et al 2002; Heckers et al 1998).

We previously found that individuals with schizophrenia show reduced activation of dorsolateral PFC during intentional encoding and retrieval of both words and faces (Barch et al 2002), as well as reduced functional laterality as a function of material type. Like control subjects, schizophrenia subjects showed greater activation of right ventrolateral PFC for faces than for words. Unlike control subjects, however, schizophrenia subjects did not show greater left ventrolateral PFC activation for words compared with faces. We hypothesized that these results reflect a failure to spontaneously use verbal processing strategies that would elicit enhanced activation for words in the prefrontal regions supporting such processes.

The levels-of-processing paradigm can be used to study the influence of strategy use on memory and brain activation. In this paradigm, participants are oriented to engage in either deep (i.e., abstract–concrete or living–nonliving judgments) or shallow (i.e., letter case or alphabetization judgments) processing of verbal stimuli, deep stimuli being associated with better recall and recognition (Craik and Lockhart 1972; Craik and Tulving 1975; for a recent review, see Craik 2002). Also, deep semantic processing at encoding preferentially activates areas in left PFC (Casasanto et al 2002; Fletcher et al 2003; Kapur et al 1994; Otten et al 2001; Otten and Rugg 2001).

Prior levels-of-processing studies in schizophrenia have shown that although people with schizophrenia show overall

From the Department of Psychology, Washington University, St. Louis, Missouri.

Address reprint requests to Aaron Bonner-Jackson, Department of Psychology, Washington University, One Brookings Drive, Box 1125, St. Louis, MO 63130; E-mail: abonnerj@artsci.wustl.edu.

Received January 13, 2005; revised April 25, 2005; accepted May 4, 2005.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2005.05.011

Table 1. Demographic and Clinical Data

Characteristic	Mean		Standard Deviation	
	Control Participants	Participants with Schizophrenia	Control Subjects	Participants with Schizophrenia
Age (years)	21.2	21.8	3.4	2.9
Sex (% male)	50	88.2		
Parents' Education (years)	15.2	15.3	2.1	2.8
Education (years)	13.8	11.9	2.6	2.0
Handedness (% right)	88.5	82.4		
Mean SAPS Global Item Score		2.4		1.4
Mean SANS Global Item Score		1.9		1.1
Poverty Symptoms		8.1		2.95
Disorganization		3.4		2.98
Reality Distortion		4.9		2.70
Atypical Medications Only (%)		82		
Combination Typical/Atypical (%)		12		
Anticholinergic Medication (%)		12		

SANS: Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

worse memory performance compared with control subjects, they benefit from being oriented toward more effective encoding strategies (Heckers et al 1998; Koh and Peterson 1978; Ragland et al 2003; Weiss et al 2003). In addition, brain activation during memory retrieval differs as a function of encoding strategy (Heckers et al 1998; Weiss et al 2003). For example, impaired hippocampal activity relative to prefrontal activity occurs during memory retrieval (Heckers et al 1998; Weiss et al 2003). Such results suggest that people with schizophrenia experience deficits in explicit recollection that subsequently require greater retrieval effort, leading to enhanced prefrontal activity. These studies have not examined, however, whether at encoding people with schizophrenia engage the neural systems associated with deep encoding and enhanced subsequent memory, such as left PFC (Brodmann area [BA] 45/47; Baker et al 2001; Buckner et al 2001; Davachi et al 2001; Fletcher et al 2003; Kapur et al 1994; Otten et al 2001; Wagner et al 1998).

The goal of this study was to examine the influence of providing encoding strategies on brain activation and recognition performance in schizophrenia subjects. We used functional magnetic resonance imaging (fMRI) to examine brain activity while schizophrenia and control subjects performed incidental encoding of words and nonfamous faces. During scanning, participants were required to make semantic (deep) or orthographic (shallow) judgments for words and gender judgments for faces (intended to elicit deep processing) at encoding, followed by a yes–no recognition test. We predicted that participants with schizophrenia would benefit as much as control subjects from deep encoding and would activate similar regions of PFC during deep encoding (when task strategy is constrained). We also investigated the effect of the deep encoding manipulation on material-specific brain activity. We hypothesized that when the deep processing conditions for faces and words were compared (i.e., with specific strategies constrained), material type would produce laterality effects in PFC among individuals with schizophrenia.

Methods

Participants

Participants were 17 individuals with schizophrenia (15 male) and 26 healthy control subjects (13 male) who met diagnostic criteria from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychological Association 1994). Subjects with schizophrenia were recruited to participate in studies of brain structure and function at the Conte Center for the Neuroscience of Mental Disorders at Washington University from a variety of outpatient treatment facilities. Control participants were recruited using local advertisements from the same community as the participants with schizophrenia. Exclusion criteria for control subjects included the presence of any lifetime history of Axis I psychiatric disorder or any first-degree relative with a psychotic disorder. Potential participants from either group were excluded for presence of any of the following: 1) meeting DSM-IV criteria for substance abuse or dependence within the past 3 months, 2) the presence of any clinically unstable or severe medical disorder, (c) head injury with documented neurologic sequelae or loss of consciousness, or (d) meeting DSM-IV criteria for mental retardation (mild or greater in severity). Demographic information is displayed in Table 1. Control and schizophrenia subjects were statistically similar on all demographic variables (p values $> .59$), with the exception of years of education ($t[41] = 2.51$, $p < .02$), for which control subjects were significantly higher than schizophrenia subjects.

All diagnoses were based on information derived from the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al 1990), which was conducted by a specially trained master's in social work–level research assistant who had access to hospital records and corroborative family sources. Additionally, an expert clinician conducted a semistructured interview and had access to all available medical records and collaborative sources but not to the SCID-IV interview results. A consensus meeting between the SCID-IV interviewer and the expert clinician determined the participant's final diagnosis.

Individuals with schizophrenia were assessed by specially trained research assistants using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983a) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1983b), and the following scores were derived: Disorganization (global scores for positive thought disorder, bizarre behavior, and attention), Reality Distortion (hallucinations and delusions), and Negative Symptoms (alogia, blunted affect, anhedonia/asociality, and anergia/amotivation). Handedness was assessed using the