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Psychiatry Research: Neuroimaging Section 107 (2001) 75–85

PSYCHIATRY RESEARCH
NEUROIMAGING

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Amygdala–hippocampal volume and verbal memory in first-degree relatives of schizophrenic patients

Gillian A. O'Driscoll[a,b,c,d,*], Patrik S. Florencio[a], Danny Gagnon[a], Anne-Lise V. Wolff[a], Chawki Benkelfat[b,c,d], Lynn Mikula[a], Samarthji Lal[b,c], Alan C. Evans[d]

[a] *The Department of Psychology, McGill University, Montreal, QC, Canada*
[b] *The Department of Psychiatry, McGill Medical School, Montreal, QC, Canada*
[c] *The Douglas Hospital Research Center, Verdun, QC, Canada*
[d] *The McConnell Brain Imaging Center, Montreal Neurological Institute, Montreal, QC, Canada*

Received 13 December 2000; received in revised form 24 May 2001; accepted 5 June 2001

Abstract

Verbal memory deficits have been related to reduced volume of medial temporal structures in several neurological and psychiatric populations, including schizophrenic patients. Impairments in verbal memory have been proposed to be a marker of risk for schizophrenia. Recently, relatives of schizophrenic patients have been reported to have reduced volume of the amygdala–hippocampal complex. In this study, we evaluate the possibility that amygdala–hippocampal volume reductions may constitute one neural substrate of verbal memory deficits in first-degree relatives. Subjects were 20 healthy first-degree relatives of schizophrenic patients and 14 demographically similar controls. Verbal memory was assessed with the Logical Memory Test. Subjects were scanned with high-resolution MRI and the images were transformed into Talairach space. Volumes of interest were amygdala–anterior hippocampus and posterior hippocampus. Relatives of schizophrenic patients had intact immediate verbal memory but significantly poorer delayed verbal memory than controls. Relatives also had significantly reduced amygdala–anterior hippocampus volumes. Across all subjects, delayed verbal memory was significantly correlated with amygdala–anterior hippocampus volume. The magnitude of the correlation did not differ between the groups. These data provide an empirical link between memory performance and volumetric abnormalities in the amygdala–hippocampal complex in the relatives of schizophrenic patients.

Keywords: Hippocampus; Neuropsychological tests; Schizophrenia; Genetic predisposition to disease

* Corresponding author. Dept. of Psychology, Stewart Biol. Sci. Bldg., McGill University, 1205 Dr. Penfield Ave., Montreal, Que., H3A 1B1, Canada. Tel.: +1-514-398-4916; fax: +1-514-398-4896.
E-mail address: gillian@hebb.psych.mcgill.ca (G.A. O'Driscoll).

0925-4927/01/$ - see front matter
PII: S0925-4927(01)00095-6

1. Introduction

Abnormalities in the volume of cortical and subcortical brain regions have been widely reported in schizophrenia (Pearlson and Marsh, 1999). Although these have been found throughout the brain, recent hypotheses of schizophrenia etiology have focused particularly on fronto–limbic systems (Cannon, 1996). Abnormalities in the amygdala–hippocampal complex are one of the best-documented neuroanatomical findings in schizophrenia (Shenton, 1996; Florencio and O'Driscoll, 1999) and have included disarrayed cytoarchitecture (Kovelman and Scheibel, 1984; Conrad et al., 1991), reductions in number of pyramidal neurons (Falkai and Bogerts, 1986) and reductions in *N*-acetyl-aspartate (NAA), a marker of neuronal integrity (Nasrallah et al., 1994; Bertolino et al., 1998). Volumetric studies of medial temporal structures have also generally found significant differences in schizophrenia (Shenton, 1996; Nelson et al., 1998; Wright et al., 2000). Recent meta-analyses of MRI studies reported a significant reduction in hippocampal volume in schizophrenic patients relative to controls (Nelson et al., 1998; Wright et al., 2000), with findings being strongest for studies combining measurements of the hippocampus and amygdala (Nelson et al., 1998).

Medial temporal structures, including the hippocampus, amygdala and surrounding cortex have been strongly implicated in long-term memory formation (Zola-Morgan and Squire, 1993). Although activation studies have indicated that both medial temporal structures and prefrontal cortex play a role in verbal memory tasks (Hasegawa et al., 1999; Heckers et al., 1998), associations between MRI volumes and memory performance have been reported almost uniquely for medial temporal lobe structures. For example, reduced medial temporal lobe volumes have been associated with verbal memory impairments in temporal lobe epilepsy (Trenerry et al., 1993; Kilpatrick et al., 1997), Alzheimer's disease (Heun et al., 1997; Libon et al., 1998) and depression (Shah et al., 1998).

Verbal memory deficits have been reported in both schizophrenic patients and their first-degree relatives. These deficits are not related to chronicity or to medication — they are found in first-episode, chronic and neuroleptic-naive schizophrenic patients (Braff et al., 1991; Hoff et al., 1992; Saykin et al., 1994; Censits et al., 1997; Ragland et al., 1996; Rushe et al., 1999). The first-degree relatives of schizophrenic patients, a proportion of whom are thought to carry susceptibility genes for schizophrenia, have also been found to have significant impairments in verbal memory (Goldberg et al., 1990; Cannon et al., 1994; Kremen et al., 1994; Faraone et al., 1995; Harris et al., 1996; Toomey et al., 1998; Byrne et al., 1999; Franke et al., 1999). The memory scores of relatives are intermediate between those of patients and controls (Goldberg et al., 1990; Cannon et al., 1994). Twin studies have shown that the genetic contribution to memory is high (Finkel et al., 1995; Swan et al., 1999) and, thus, verbal memory deficits may reflect inherited differences in the structure and function of medial–temporal lobe regions.

Recently, volumetric reductions in medial temporal lobe structures have been reported in the first-degree relatives of schizophrenic patients (Keshavan et al., 1997; Lawrie et al., 1999; Seidman et al., 1999). In these studies, the reductions have been found in the amygdala–hippocampal complex. The reductions that have been reported in first-degree relatives (approx. 10%) are relatively small compared with those observed in neurological patients (20–50%) (Trenerry et al., 1993; Kilpatrick et al., 1997; Heun et al., 1997; Libon et al., 1998) but could contribute to the reported deficits in memory.

The current study compared verbal memory and amygdala–hippocampal complex volumes in first-degree relatives and controls, and assessed the relationship between amygdala–hippocampal volumes and verbal memory performance.

2. Methods

2.1. Subjects

Thirty-four subjects took part in the study. Subjects were first-degree relatives of schizophrenic