



The impact of familial risk for schizophrenia or bipolar disorder on cognitive control during episodic memory retrieval

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ABSTRACT

Episodic memory impairment is a robust correlate of familial risk for schizophrenia (SZ) and bipolar disorder (BD); still much is unknown about the processes that underlie this deficit and how they may be implicated in BD and SZ. We examined the possibility that (a) episodic memory impairment may arise from abnormalities in the cognitive control of interference between task-relevant and task-irrelevant memories during retrieval; inability to suppress task-irrelevant representations could give rise to intrusions of inappropriate memories and increased rate of forgetting, (b) cognitive control deficits during retrieval may be differentially affected by familial predisposition to SZ or BD. We examined episodic memory in relatives of patients with SZ (SZ-R) ($n = 15$) or BD (BD-R) ($n = 17$) compared to healthy controls ($n = 23$) using the California Verbal Learning Test (CVLT) and the Doors and People Test (DPT). All relatives were free of any psychiatric morbidity and were matched to controls on age, sex, educational achievement and general intellectual ability. During the CVLT, both relatives' groups made significantly more perseverative recall errors than controls. However, intrusion errors were significantly increased in SZ-R only. SZ-R also showed increased rate of forgetting in the DPT while BD-R were comparable to controls. Familial predisposition to SZ, compared to that of BD, was associated with significantly greater impairment in cognitive control processes during episodic memory retrieval with some evidence of specificity for SZ in connection with mechanisms relating to increased forgetting.

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1. Introduction

Disruption in memory systems is a replicable finding in patients with schizophrenia (SZ) and bipolar disorder (BD) particularly with respect to episodic memory (Aleman et al., 1999; Torres et al., 2007). Episodic memory refers to the ability to recall information through personal experience (Tulving, 1983). Effect sizes for episodic memory deficits have been found to be large for patients with SZ (range 1–1.27) and moderate to large for patients with BD (range 0.59–0.85) (Skelley et al., 2008; Bora et al., 2009; Lefebvre et al., 2010). Episodic memory impairment is also associated with familial predisposition as unaffected relatives of patients with SZ or BD also show deficits of moderate effect size (range 0.44–0.65 for SZ and 0.33–0.53 for BD) (Snitz et al., 2003; Whyte et al., 2005; Arts et al., 2008; Skelley et al., 2008; Bora et al., 2009; Glahn et al., 2010; Lefebvre et al., 2010).

Episodic memory tasks typically involve a learning condition, where participants are given information (usually pictures or words) to 'encode' into memory, and a retrieval condition, where participants are requested to recall this information. Successful retrieval is thought to rely on processes of cognitive control (Anderson and Neely, 1996) implemented through the coordinated engagement of the hippocampus (and adjacent cortical regions), the anterior cingulate and the prefrontal cortex (Nyberg et al., 1996; Fletcher et al., 1997; Tulving, 2002; Kuhl et al., 2008; Schott et al., 2011). Within this network the ability to recall information correctly relies on cognitive control processes in order to overcome competition (or interference) between task-relevant and task-irrelevant memories (Monsell, 1978; Jonides et al., 1998). Inability to suppress task-irrelevant representations could give rise to intrusions of inappropriate material during recall as well as increased rate of forgetting (Kuhl et al., 2007). It has been proposed that the mechanisms underpinning interference control during episodic memory retrieval are not specific to this domain but reflect shared inhibitory processes that manage interference across tasks (Hamilton and Martin, 2005).

We (Frangou et al., 2006) and others (Krabbendam et al., 2005; Bora et al., 2010) have previously provided evidence for dysfunction across a number of cognitive control tests being significantly greater

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in patients with SZ than in patients with BD. More recently, we have reported that unaffected relatives of SZ patients demonstrate significantly greater impairment in cognitive control than relatives of BD patients as implied by increased intrusion errors during cued word production and reduced inhibition of task-irrelevant responses (Christodoulou et al., 2011). Here we extend the comparative examination of the effect of familial predisposition to SZ or BD in the same sample by focusing on aspects of cognitive control during episodic memory using the California Verbal Learning Test (CVLT; Delis et al., 1987) and the Doors and People Test (DPT; Baddeley et al., 1994) as probes. The CVLT is a popular test of episodic memory which allows the examination of susceptibility to interference based on measures of recall errors while the DPT provides estimates of the rate of forgetting. We hypothesised that unaffected relatives of patients with SZ will show greater susceptibility to interference as indexed by increased recall errors and increased rate of forgetting compared to unaffected relatives of BD patients.

2. Methods

2.1. Participants

Seventeen first-degree relatives of patients with BD (BD-R), 15 first-degree relatives of patients with SZ (SZ-R) and 23 demographically matched healthy controls (HC) were drawn from participants enrolled in two ongoing departmental studies (Frangou et al., 2005; Frangou, 2009; Kempton et al., 2009; Walterfang et al., 2009; Takahashi et al., 2010; Forcada et al., 2011; Kumar et al., 2011; Lelli-Chiesa et al., 2011; Perrier et al., 2011; Pompei et al., 2011a, 2011b; Ruberto et al., 2011).

For this analysis, we only included relatives without any current or lifetime personal history of any Axis I disorder based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DAM-IV) (American Psychiatric Association, 1994) and healthy controls without any personal or family history (up to 2nd degree) of Axis I disorders. Exclusion criteria for all participants included (a) head trauma resulting in loss of consciousness, (b) personal history of neurological or medical disorders, (c) family history of hereditary neurological disorders, and (d) drug or alcohol abuse in the preceding 6 months as defined by the DSM-IV. Level of education was rated on a 5-point scale ranging from 1 (no educational qualification), 2 ("O" levels), 3 ("A" levels), 4 (university degree or equivalent) to 5 (post graduate university level qualifications). Additionally, relatives were sampled from different families and were therefore unrelated. Therefore the size of the relatives' sample was restricted by necessity to those fulfilling all these requirements.

Ethical approval was obtained from the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee. Written informed consent was obtained from all participants.

2.2. Clinical assessment

All participants (relatives and controls) underwent the same diagnostic assessment using the Structured Clinical Interview for DSM-IV Axis-I Disorders (First et al., 2002) administered by trained psychiatrists. Family history was assessed using Family Interview for Genetic Studies (FIGS, Maxwell, 1992). Psychopathology was further assessed on the day of their cognitive testing with the Brief Psychiatric Rating Scale (BPRS, Ventura et al., 1993), the 21-item Hamilton Depression Rating Scale (HDRS, Hamilton, 1960) and the Young Mania Rating Scale (YMRS, Young et al., 1978).

2.3. Neuropsychological assessment

All participants were tested by the same psychologist (TC). Tests were administered in fixed order a single session. The California Verbal Learning Test (CVLT; Delis et al., 1987) is designed to assess verbal learning, recall and recognition. Participants listen to two lists (List A and B) of 16 words from 4 semantic categories. First they are presented with list A and are asked to recall the items of the list over 5 trials. List B is presented once, immediately after the fifth recall of List A. Short free and category cued recall are assessed immediately afterwards. Long delay free and semantically cued recall and recognition as assessed after a 20 min interval. During recognition participants listen to 44 items and are asked to identify those previously presented. Outcome variables include words correctly recalled from List A after the 1st and over the 5 presentations, words correctly recalled from List B, words correctly recalled from List A after the short delay (free and cued) and after the long delay (free and cued) and words correctly recognised. Errors can occur in the form of intrusions (when participants "recall" a word that was not on the list) and perseverations (when participants repeat a word more than once). The Doors and People test evaluates both verbal and visual memory (DPT; Baddeley, et al., 1994). In the visual recognition condition participants are asked to memorise a series of coloured photographs of doors and then to identify each target door from a set of four doors of varying similarity. In the visual recall condition, participants first copy four patterns and then

are asked to reproduce them from memory both immediately and after a delay. In the verbal recognition condition participants read aloud a series of names and are then required to identify each name from sets of four. In the verbal recall condition, participants are asked to learn the names of four people, a doctor, a postman, a minister, and a newspaper boy and are then asked to recall them both immediately and after a delay. The overall memory scaled score and the verbal and visual forgetting scaled scores were used in this analysis.

We used the Wechsler Adult Intelligence Scale—Revised (WAIS-R, Wechsler, 1981) Vocabulary subtest to obtain an estimate of current intelligence quotient (IQ). The test requires giving brief and precise definitions of concrete and abstract words presented in order of increasing difficulty.

2.4. Statistical analysis

The three groups (SZ-R, BD-R, HC) were compared in terms of demographic characteristics and psychopathology scores using analysis of variance or chi square tests as appropriate.

Outcome measures from the CVLT and DPT were entered as dependent variables into separate univariate or multivariate or repeated measures analyses of covariance with group as the independent factor, BPRS and IQ scores as covariates. When the overall model indicated an effect of group, this was followed-up by pairwise *t*-tests with Bonferroni correction. Effect sizes for all neuropsychological measures comparing BD-R and SZ-R to HC were calculated as Cohen (1988).

3. Results

3.1. Demographic and clinical characteristics

Demographic information and psychopathology ratings for all participants are shown in Table 1. There were no group differences in age ($p = 0.21$), sex ($p = 0.97$), educational level ($p = 0.75$) and IQ ($p = 0.33$). The three groups differed in terms of total HDRS, YMRS and BPRS (all $p < 0.0001$); this effect was driven primarily by the SZ-R who were statistically more symptomatic than HC on all scales. The BPRS score were highly correlated with those of the other two scales ($r > 0.65$, $p < 0.0001$) and was chosen as a covariate in all analyses as it is more suitable for non-clinical populations.

3.2. Neuropsychological performance

Details of neuropsychological performance are shown in Table 2.

3.2.1. California Verbal Learning Test (CVLT)

In terms of learning for List A, repeated measures analyses showed no significant effect of group ($F_2 = 0.74$, $p = 0.48$) or trial by group interaction ($F_2 = 0.60$, $p = 0.51$); there was a significant effect of IQ ($p = 0.003$) and BPRS score ($p = 0.002$) but neither showed an interaction with group ($p > 0.80$). Multivariate analysis of short free and cued recall and delayed recall showed no effect of group ($F_{8,94} = 0.84$, $p = 0.56$) or BPRS ($F_{4,46} = 1.10$, $p = 0.40$); there was a significant effect of IQ ($F_{4,46} = 2.77$, $p = 0.03$) but no interaction with group ($p = 0.74$). As these results were negative, post-hoc power calculations were conducted which indicated that at an alpha

Table 1
Clinical and demographic characteristics of the sample.

	Relatives of patients with schizophrenia ($n = 15$)	Relatives of patients with bipolar disorder ($n = 17$)	Healthy controls ($n = 23$)
Age (years)	45.8 (14.2)	38.7 (13.4)	39.0 (13.4)
Educational level	3.5 (0.9)	3.6 (0.9)	3.7 (0.9)
Sex (female:male)	11:4	13:4	17:6
Siblings:parents: offspring	5:10:0	6:3:8	–
HDRS	0.8 (0.7) ^a	0.1 (0.3) ^a	0.08 (0.2) ^a
YMRS	0.7 (1.03) ^b	0.4 (0.7) ^c	0.1 (0.3) ^c
BPRS	25.6 (0.8) ^d	24. (1.1) ^d	24.2 (0.4)

Apart from sex data shown are mean (standard deviation); HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; BPRS: Brief Psychiatric Rating Scale.^aRange = 0–2.^bRange = 0–3.^cRange = 0–1.^dRange = 24–28.

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