



Functional connectivity pattern during rest within the episodic memory network in association with episodic memory performance in bipolar disorder

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ABSTRACT

In this study, we sought to examine the intrinsic functional organization of the episodic memory network during rest in bipolar disorder (BD). The previous work suggests that deficits in intrinsic functional connectivity may account for impaired memory performance. We hypothesized that regions involved in episodic memory processing would reveal aberrant functional connectivity in patients with bipolar disorder. We examined 21 patients with BD and 21 healthy matched controls who underwent functional magnetic resonance imaging (fMRI) during a resting condition. We did a seed-based functional connectivity analysis (SBA), using the regions of the episodic memory network that showed a significantly different activation pattern during task-related fMRI as seeds. The functional connectivity scores (FC) were further correlated with episodic memory task performance. Our results revealed decreased FC scores within frontal areas and between frontal and temporal/hippocampal/limbic regions in BD patients in comparison with controls. We observed higher FC in BD patients compared with controls between frontal and limbic regions. The decrease in fronto-frontal functional connectivity in BD patients showed a significant positive association with episodic memory performance. The association between task-independent dysfunctional frontal-limbic FC and episodic memory performance may be relevant for current pathophysiological models of the disease.

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1. Introduction

Patients suffering from bipolar disorder (BD) shows a number of severe cognitive symptoms during acute depressive or manic states including the domains of attention, memory and executive function (Bora et al., 2009). One cognitive domain that has been frequently reported to show resistant deficits in acute (Martinez-Aran et al., 2000; Sweeney et al., 2000; Quraishi and Frangou, 2002) and remitted (Deckersbach et al., 2004; Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009) states is episodic memory. Episodic memory is part of the declarative memory system and encompasses the storage and intentional

recall of events from a person's life in an ascertained temporal and spatial context (with detailed memories of the recalled event) (Tulving, 1992). The human memory system is hierarchically organized, with long-term memory at the top, declarative memory and non-declarative at a secondary level (Squire and Zola-Morgan, 1991). The special characteristic of the episodic memory is that it comprises semantic as well as emotional information. The investigation of episodic memory deficits and their underlying functional representation in neuronal structures is of relevance for the daily functioning of the patients, as those deficits lead to job-related problems and social withdrawal. On the other hand, the involvement of emotionally salient information during episodic memory processing is of importance for further clinical symptoms of BD, which are often related to affective dysregulation. Episodic memory may be more related to 'hot cognition' (= cognition with emotional involvement) than to 'cold cognition' (= lack of emotional influence) (Roiser, 2013). However, the emotional influence may influence the underlying neuronal activation pattern.

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Most of the existing research on episodic memory performance in BD has focused on learning and recall tests in the verbal domain. However, of interest are potential associations between reduced episodic memory performance and the underlying neural activation patterns (Townsend et al., 2010), which can be measured with functional magnetic resonance imaging (fMRI). During episodic memory encoding and retrieval, a fronto-temporo-parietal neuronal network is involved. During encoding, predominantly frontal and parietal association cortices are active, together with limbic activation (Kellermann and Piefke, 2013). During retrieval, the orbitofrontal and the prefrontal cortex, medial temporal regions, the gyrus cinguli and the precuneus are active (Kellermann and Piefke, 2013).

Current episodic memory task-related fMRI findings in BD patients have revealed aberrant functional connectivity between ventral prefrontal and limbic brain regions (Yurgelun-Todd et al., 2000; Blumberg et al., 2003; Kronhaus et al., 2006; Oertel-Knöchel et al., 2013; Oertel-Knöchel et al., 2014) or focused on hippocampal alterations (Krug et al., 2014). These results have to be considered in the context that the episodic memory system requires brain activation that is related to both cognitive and emotional processing. Of interest is the question whether aberrant functional patterns during episodic memory encoding and retrieval represent emotional deregulation, or cognitive deficits, or both. Moreover, the question arises whether aberrant functional connectivity between frontal and limbic brain regions is related to specific symptoms of the disorder, such as memory deficits, or is a trait marker independent of particular symptoms. Findings from fMRI studies concerning other aspects of memory in BD have shown that BD might be related to a pattern of reduced prefrontal activation together with a disinhibition of subcortical structures, such as the amygdala, striatum and thalamus (Adler et al., 2004; Monks et al., 2004; Lagopoulos and Malhi, 2007; Drapier et al., 2008; Phillips et al., 2008; Townsend et al., 2010; Stegmayer et al., 2014).

In the previous study of our group, we identified brain regions that showed significant functional alterations during episodic memory performance in BD patients (Oertel-Knöchel et al., 2013). The study revealed decreased frontal activation during encoding and retrieval, and decreased occipital (cuneus) and limbic (parahippocampal gyrus) activation during retrieval in BD patients compared with controls, patterns of activity that were directly associated with poor episodic memory performance.

Current knowledge about whether these effects are also present in task-naïve or off-line periods of brain dynamics is scarce. In this study, we investigated the connectivity of episodic memory networks in the resting state of BD patients compared with controls. Overall, there are relatively few resting state fMRI studies in BD patients, but there is rapidly growing interest in the topic (Anand et al., 2009; Chepenik et al., 2010; Ongur et al., 2010; Chai et al., 2011; Anticevic et al., 2013; Mamah et al., 2013; Meda et al., 2013; Torrisi et al., 2013; Das et al., 2014; Liu et al., 2014). The general approach in those studies was based on predefined seed regions in certain limbic areas and the prefrontal cortex, in order to assess intrinsic resting state connectivity of frontal-limbic functional networks (Anticevic et al., 2013; Mamah et al., 2013; Meda et al., 2013; Torrisi et al., 2013; Liu et al., 2014) or the default mode network (DMN) (Ongur et al., 2010; Meda et al., 2013). Overall, the current literature shows variable results, with hypo- as well as hyper-functional connectivity between frontal and limbic brain regions in BD patients in comparison with controls. These findings were interpreted as a failure in the disinhibition of limbic areas and limbic-frontal connections that may underlie affective symptoms (Chepenik et al., 2010) or cognitive deficits (Chai et al., 2011).

However, none of these previous studies have directly addressed memory performance and intrinsic functional connectivity in brain regions directly selected from activation pattern of participants during an episodic memory task. Therefore, a novel aspect

of our study is that we examined resting state functional connectivity using seed regions that showed activation differences between BD patients and controls during a previous fMRI study of episodic memory in the same subject sample. We hypothesized that BD patients would show aberrant resting state functional connectivity with areas already showing episodic memory task-related activation differences compared with controls. We further expected that changes in the functional architecture of the episodic memory network would be directly associated with episodic memory performance.

2. Methods

2.1. Participants

We studied 21 outpatients with bipolar disorder (mean age [M]=35.67 years [SD]=10.68) diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994). All patients were in a remitted state of the illness at the time of study and did not have any comorbid axis I or II disorders (including substance use disorders). We ensured the remitted state using the German version of the Beck Depression Inventory II (BDI II) (Hautzinger et al., 2006) and the German version of the Bech-Rafaelsen Mania Scale (BRMAS) (Bech, 1981) cut-off scores for clinical relevance and the DSM-IV criteria for acute episodes. Remitted state was defined by a BDI II score of < 18 and a BRMAS score of < 7. None of the patients fulfilled the cut-off scores or the DSM-IV criteria for an acute depressed or manic episode at the time of study. We also ensured that the BD patients had been on stable medication for at least 4 weeks before measurement. The psychiatric medications included mood stabilizers ($n=21$) and in some cases additional antidepressants ($n=3$) (see Table S2, Supplemental material). We computed medication scores according to the method of Almeida et al. (Almeida et al., 2009). In sum, the patient group had a mean duration of medication of 6.26 ($SD=6.09$) years (see Table 1 for further details).

We also examined a group of healthy controls ($n=20$; mean age=36.90 years [SD]=11.06) who were matched with the patient group for age, gender and education. Exclusion criteria for control participants were current drug abuse, neurological disease, any history of psychiatric disorders including axis I and axis II disorders according to DSM-IV, and an inability to provide informed consent. We ensured that none of the controls had any positive family history of affective or psychotic disorder, and confirmed the patients' diagnosis and absence of comorbid disorders using the Structured Clinical Interview for DSM-IV (SCID-I and SCID-II; German version: Wittchen et al., 1996). To ensure that the main results were not biased by general intelligence, all participants performed the MWT-B (Mehrfachwahl-Wortschatz-Test; Lehrl, 2005), the German equivalent of the "Spot-the-Word test" (Baddeley et al., 1993). Statistical tests (analysis of variance, Scheffé post-hoc contrast analyses, chi-square-tests) for differences between the groups regarding age, general intelligence, handedness and parental education revealed no significant group differences (all p 's > 0.05).

The anatomical MRI scans of all participants were reviewed by a neuroradiologist who did not find any underlying clinically relevant pathology. Participants were provided with a description of the study and gave written informed consent before participating. Experimental procedures were approved by the ethical board of the Medical Department of the Goethe-University, Frankfurt/Main, Germany. The participants were part of another behavioral and fMRI study of the working group (Oertel-Knöchel et al., 2013).

2.2. Assessment of cognitive and clinical data

The episodic memory task that was used in our previous study contained an encoding and a retrieval phase; during encoding, participants had to learn 20 sequentially presented words (verbal memory). During retrieval, participants had to recognize the learned items using a recognition task. The tasks were performed during fMRI scanning with the same sample as in the current study. The accuracy of all participants was recorded using the presentation® software to create logfiles of each participant's performance. The task-related fMRI data were analyzed for group differences in encoding and retrieval, using only the correctly recalled items (see further details: Oertel-Knöchel et al., 2013).

We also assessed episodic memory performance using the California Verbal Learning Test (CVLT) (Niemann et al., 2008), which includes an interference and a recognition list. We used the following parameters of the CVLT assessment: *delayed free recall I* (DFR I) and *delayed free recall II* (DFR II).

All participants were also screened for their current mental state using the Positive and Negative Affect Schedule (PANAS) (Krohne et al., 1996). For the PANAS, two scores were computed: the *positive affect* (PANAS PA) and the *negative affect* (PANAS NA).

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