State- and trait-related deficits in sustained attention in bipolar disorder

Abstract  Investigation of neuropsychological functioning in bipolar disorder provides a potential link from the prominent cognitive symptoms of the disorder to the underlying neural mechanisms. Continuous performance measures of sustained attention have yielded consistent findings in bipolar disorder patients. There are impairments that appear to be both state- and trait-related. Impaired target detection may represent one of the most sensitive markers of illness course in bipolar disorder. It is unrelated to residual mood symptomatology and medication status, and is present in patients with good functional recovery. The impairment in target detection is exacerbated in the manic state, and is accompanied by an increased rate of false responding. Sustained attention deficit is present early in the course of the disorder, but becomes more pronounced with repeated episodes. This cognitive profile, of an early-onset, state-modulated, trait marker, is distinct from the profile of attentional disruption seen in schizophrenia or unipolar depression. The state- and trait-related impairments may be differentially associated with the ascending dopamine and noradrenaline projections.

Key words  bipolar disorder · neuropsychology · attention · vigilance · mania

Introduction

In the Kraepelinian distinction between bipolar disorder and schizophrenia, a defining feature of bipolar disorder is the apparent recovery of function between episodes, contrasting with the deteriorating course seen in schizophrenia. However it is now increasingly recognised that recovery in bipolar disorder is not necessarily complete: sub-clinical levels of affective symptomatology may persist, and social and occupational functioning remain impaired (Dickerson et al. 2001; Dion et al. 1988; Scott 1995). Studies have also begun to examine cognitive functioning in the discrete phases of bipolar disorder (see Bearden et al. 2001; Martinez-Aran et al. 2000; Murphy and Sahakian 2001; Quraishi and Frangou 2002 for reviews). By cognitive function we here mean what is neuropsychologically measurable. Such measures promise fruitful links to the evolving understanding of normal neurocognition.

Of all the domains of neurocognition examined in bipolar patients, sustained attention appears of unusual interest. Its investigation has yielded particularly consistent results, and may provide an important foundation for a clinical understanding of cognitive deficits in bipolar disorder. The purposes of the present review are to examine 1) the state and trait profile of sustained attention deficits in bipolar disorder, 2) the association of sustained attention deficits with the clinical course of bipolar disorder, 3) the selectivity of sustained attention deficit to bipolar disorder, and 4) the cognitive and physiological mechanisms of these deficits.

The assessment of sustained attention

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cessing of external stimuli. It can be measured in human subjects using a variety of Continuous Performance Tests (CPT), of which there are several well-validated examples. In these tasks, subjects are required to monitor a stream of stimuli (such as digits or letters), and to make a response (such as a key press) whenever a specified target appears. Stimuli are presented at a rapid rate for a period of several minutes, and targets occur unpredictably so that to perform well, subjects must focus attention on a monotonous task and avoid distraction from either internal thoughts or extraneous environmental stimuli. Healthy performance requires an adequate level of *arousal* (Parasuraman 1984, 1998), associated with the ascending neurotransmitter projections from subcortical structures to the cortex. In addition, CPTs also demand a level of *executive control* in order to i) hold specified targets in working memory, ii) inhibit task-irrelevant stimuli competing for neural resources, and iii) inhibit responses to task-relevant stimuli resembling targets (Braver et al. 2002; Manly and Robertson 1997).

In the original CPT (Rosvold et al. 1956), subjects were required to monitor a stream of letters, and to respond either to the letter X (the X-CPT), or in a more difficult version, to the letter X only when preceded by the letter A (the AX-CPT). A more recent version of this task uses degraded visual stimuli to increase the demands on visual processing and arousal (Nuechterlein and Asarnow 1993). In the Rapid Visual Information Processing task (RVIP, Cambridge Cognition Ltd, Cambridge, U.K.), subjects monitor a stream of digits for specified sequences, e.g. 3–5–7. Digits are presented at the rate of 100 per minute, for 7 minutes. Task difficulty can be manipulated by presenting digits at a faster or slower rate, and working memory load can be manipulated by increasing or decreasing the number of target sequences. In a third task, the IMT-DMT (Immediate Memory Test – Delayed Memory Test; Dougherty 1999), subjects view 5-digit strings (e.g. 34534) for short durations (0.5 seconds), and are required to respond whenever consecutive strings are identical. The demands for inhibitory control are increased in this task by presenting strings differing by only one digit (e.g. 34524) from the previous string. The basic CPT template therefore provides the opportunity to manipulate several cognitive parameters including working memory load, inhibitory control, and visual processing (see Elvevag et al. 2000 for a demonstration of this).

CPTs are less sensitive to practice effects than traditional measures of executive function such as the Wisconsin Card Sort Test or the ID/ED shift task, and are therefore better suited for use in cross-over designs, as might be employed in pharmacological challenge or clinical treatment studies. Similar performance indices are derived from all CPTs: the percentage of targets correctly detected, the average latency on correct responses, and the total number of commission errors or false alarms. The rate of false responding partly confounds the level of target detection: an increase in indiscriminate responding will increase the number of both correct and incorrect responses. For this reason many studies combine these measures using signal detection analysis to derive the independent variables d-prime (target sensitivity) and beta (response bias) (Cornblatt and Keilp 1994). Target detection on CPTs also tends to decrease over the duration of a task (the ‘vigilance decrement’), providing an additional performance variable that may be independent of target detection at the start of the task (Koelega 1993).

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**Sustained attention in bipolar disorder**

CPTs have been employed in several recent investigations in patients with bipolar disorder (BPD). Clark et al. (2001) included the RVIP in a broad cognitive test battery assessing executive function, decision-making, verbal learning and memory in 15 acutely manic inpatients, compared with 30 healthy matched controls. Whilst the manic patients were impaired relative to controls on virtually all cognitive measures, discriminant function analysis showed that target detection on the RVIP and the verbal learning score (on the California Verbal Learning Test) were the cognitive measures that best distinguished the two groups, correctly classifying 91% of subjects overall, and 87% of manic subjects. As well as impaired target detection on the RVIP, manic patients made more false alarms and responded slower than controls. This study therefore showed that sustained attention deficit is one of the most robust cognitive deficits in the manic state. The increased false responding also appears to relate to aspects of the mental state in mania such as impulsivity and distractibility, although our sample was not large enough or heterogeneous enough to demonstrate it.

In a follow-up study, Clark et al. (2002) administered the same cognitive test battery to an independent group of 30 euthymic patients with bipolar disorder. Mild affective symptoms remained present in the euthymic state, and after controlling for these symptoms, impaired target detection on the RVIP was the only significant deficit in the bipolar group relative to controls. Other group differences in verbal learning and attentional set shifting were largely attributable to these mild affective symptoms, for which few other studies have controlled (see also Ferrier et al. 1999). There was evidence that the euthymics showed a greater vigilance decrement than controls, and that response latency was also slowed. However, there were no differences from controls in rates of false alarms in the euthymic patients implying recovery from the manic state (Fig. 1).

The studies in euthymia and mania together indicate that a sustained attention deficit represents a trait marker in bipolar disorder. Thus, the degree of sustained attention deficit failed to correlate with symptom ratings on the Young Mania Rating Scale (YMRS) in the acutely manic patients (Clark et al. 2001). However, it was clear that the degree of impairment was slightly