Eur Arch Psychiatry Clin Neurosci (2004) 254 : 61–68 DOI 10.1007/s00406-004-0460-y

SPECIAL ISSUE

Luke Clark · Guy M. Goodwin

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

The attentional system of the human brain appears to comprise several processes that are likely mediated by independent, albeit interacting, neurobiological systems. Separate mechanisms have been proposed for divided attention, selective attention, shifting attention, and sustaining attention (Desimone and Duncan 1995; Posner and Petersen 1990; Robbins 1998). Sustained attention is close to what folk psychology would call concentration and is usually assumed to form the basis for more complex cognitive tasks requiring effortful pro-

L. Clark
Department of Experimental Psychology
University of Cambridge, UK

Prof. G. M. Goodwin (✉)
University Department of Psychiatry
Warneford Hospital
Headington
Oxford OX3 7JX, UK
Tel.: +44-1865226451
E-Mail: guy.goodwin@psych.ox.ac.uk

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).

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 distractbility, 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

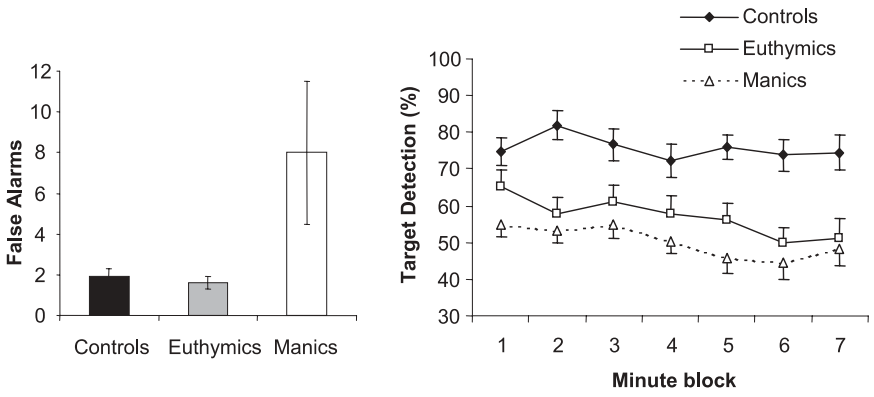

Fig. 1 Sustained attention in bipolar disorder, on the seven-minute Rapid Visual Information Processing (RVIP) task. Acutely manic patients (n = 15) make more false alarms on the task than both controls (n = 30) and euthymic bipolars (n = 30), but deficits in target detection are present in both the manic and euthymic groups. See Clark, Iversen and Goodwin (2001, 2002)

greater in the manic patients than the euthymics: the effect size for the percentage of targets detected was 1.48 for the manics–controls comparison and 0.96 for the euthymics–controls comparison. Two further studies have also produced findings that are highly complementary to our data. Liu et al. (2002) tested a group of 15 bipolar patients at inpatient admission, and a second time within days of discharge. Whilst clinical state at the time of admission was not specified, these patients were severely impaired on the degraded stimulus CPT, both in terms of target sensitivity and response bias (they detected fewer targets and made more false alarms). At discharge, target detection improved but patients remained deficient relative to a large normative sample. In the same study, a further 53 remitted bipolar outpatients were also tested on one occasion only. The combined group of remitted bipolars were impaired on target sensitivity but showed normal rates of false responding. Target sensitivity was not significantly associated with symptom ratings on the YMRS or Hamilton Depression Scale. A second study by Swann et al. (2003) tested separate groups of euthymic (n = 25) and manic (n = 14) BPD patients on the IMT-DMT (described above). Both euthymic and manic groups detected significantly fewer targets compared to controls, and the manic patients were more impaired, albeit non-significantly. Commission errors on the task showed that only the manic patients were more impulsive, indicating that CPTs tap both state- and trait-associated deficits in bipolar disorder, which may be associated with independent physiological mechanisms.

CPT impairments in the manic state have also been demonstrated by Sax et al. (1998, 1999) and Seidman et al. (2002). In a small sample, Sax et al. (1999) demonstrated that the degree of impairment correlated with MRI volumes of frontal cortex and hippocampus. Structural volumes are assumed to be temporally stable, supporting the proposal that sustained attention tasks tap a trait-related construct in bipolar disorder. CPT deficits in remitted BPD were also found by Addington & Addington (1997) and Wilder-Willis et al. (2001). In the former study, no symptom ratings were provided, whilst the latter study showed no correlation between CPT performance and YMRS score in a mixed group of patients who were partially- or fully-remitted from manic episodes.

The studies discussed in this section form a strikingly consistent body of research indicating that sustained attention deficit is present in the euthymic state of bipolar disorder and is exacerbated during episodes of mania. The degree of impairment typically does not correlate with symptom ratings, which is likely to be because of the over-riding trait impairment. There is, however, a paucity of studies examining BPD patients in the depressed phase on measures of sustained attention. Sax et al. (1998) reported that there were no significant differences on the degraded stimulus CPT between bipolar patients hospitalised for mania or depression, but only the combined group data were presented. Rund et al. (1992) reported CPT impairments in 19 BPD patients, including 16 in the depressed phase. Unfortunately this study did not report performance means or ratings of depressive symptomatology. Further research could helpfully confirm that in the depressed phase, as well as the manic phase, sustained attention deficits are exacerbated relative to remission.

Sustained attention and the clinical course of bipolar disorder

We reported a specific deficit in sustained attention in the euthymic state of bipolar disorder (Clark et al. 2002). Performance on difficult measures of executive function, such as the Tower of London planning task, the Iowa Gambling Task, and a self-ordered Spatial Working Memory task were largely preserved. Other group differences between bipolars and controls in verbal learning (CVLT) and attentional set shifting (ID/ED shift) were attributable to mild affective symptoms persisting in the euthymic state. The *absence* of deficits in these measures may be surprising in the wake of other studies suggesting that performance in euthymic patients may be impaired on just these measures in some bipolar I groups. For example, in one highly comparable recent study and despite identical control measures, performance on the CVLT was impaired more than in our patient group (Cavanagh et al. 2002). Indeed, there is a

common view that performance on a range of tests tends to be abnormal in recovered bipolar patients (see, for example, Bearden et al. 2001).

The patient group we studied had suffered severe bipolar I episodes, but were relatively high functioning: the majority were engaged in current employment, and were educated, on average, to degree level. Clearly multiple cognitive impairments are not a necessary part of the clinical picture in bipolar disorder, but attentional deficits are. Our central conclusion is, therefore, that sustained attention is the most sensitive marker of cognitive impairment yet described in bipolar disorder. This is consistent with the other studies in different clinical case series, which have indicated that deficits in learning and executive function do exist in fully-remitted patients independent of residual symptoms (Ferrier et al. 1999; Rubinsztein et al. 2000; van Gorp et al. 1998; Zubieta et al. 2001).

There are usually correlations between the degree of global cognitive dysfunction and some clinical indices of the progression of the disorder (Kessing 1998; van Gorp et al. 1998). The number of episodes of mania or depression, and the lifetime months spent in manic or depressed episodes tend to be more associated with the degree of cognitive impairment than the total duration of the illness, i. e. months since diagnosis (Kessing 1998; van Gorp et al. 1998). This indicates that the illness episodes themselves may have a long-term detrimental effect on cognitive function. Relatively few of the studies using CPTs in bipolar disorder have reported associations with clinical course. The findings of Liu et al. (2002) and Swann et al. (2003) are broadly consistent with the wider cognitive literature, showing no significant associations between CPT performance and the duration of illness or the age of onset, but neither study examined the association with number of episodes. Clark et al. (2002) found that RVIP target detection was negatively correlated with number of manic episodes, number of depressed episodes, and duration of illness, but there was no association with number of hospitalisations. The mechanism whereby repeated episodes may damage cognitive function is unknown. Both mania and depression elevate cortisol levels, so one well-known mechanism could be hypercortisolemia perhaps affecting the hippocampus (Altshuler 1993). This might explain mnemonic difficulties in the more chronic patient groups. However, the impact on sustained attention and the pattern of its impairment could imply noradrenergic dysfunction (Clark et al. 2002 and see below).

If sustained attention does progressively deteriorate with the course of bipolar disorder, this leaves open the question of whether impairment is present at illness onset. In a post-hoc analysis, Clark et al. (2002) selected the eight euthymic patients from their sample of 30 patients with shortest illness durations: less than 40 months since diagnosis and no more than two hospitalisations. RVIP deficits remained present in this subgroup, despite the association in the whole group with clinical progression. Identification of precisely when these deficits emerge is a challenge for future research. CPT deficits *during* the first episode were demonstrated in affective disorder patients with psychotic features, mostly with bipolar diagnoses (Albus et al. 1996). From the low average HAM-D score in that study, one could infer that these patients were mostly manic at the time of testing. Sax et al. (1998), in contrast, found no statistically significant CPT deficit in patients with affective psychosis (mostly bipolar) *on recovery* from their first hospitalisation. However, the remitted patients were more impaired on average, and the effect size for this difference was 0.67, which is compatible with a moderate effect. Therefore this study was probably underpowered to detect CPT deficits in the euthymic state. Sustained attention deficits could antedate the first episode of bipolar disorder or could emerge as a consequence of rapid structural reorganisation at the first episode. Studies in unaffected groups at high risk for bipolar disorder, such as first-degree relatives of bipolar patients, provide the most straightforward and direct way to test these hypotheses at the current time.

The effect of medication on cognitive functioning is a ubiquitous concern in neuropsychological research in bipolar disorder. The vast majority of euthymic patients in the studies discussed above were receiving treatment with mood stabilisers, and when studying acute mania, it is not usually possible to engage patients in cognitive testing until antipsychotic treatment has begun. The sedative effects of neuroleptics and benzodiazepines on general arousal are a particular concern when assessing sustained attention. However, the wide range of medication regimes and dosages across the reported studies makes it unlikely, at face value, that a consistent deficit in sustained attention deficit is fully attributable to one side effect or pharmacological action shared by many treatments. We showed that the RVIP deficit in the euthymic state did not correlate with lithium dosage or months treated with lithium, did not differ between patients on (n = 19) and off (n = 11) lithium, and remained significant in those patients off lithium (n = 11) (Clark et al. 2002). In the manic state, we showed that the RVIP deficit did not correlate with antipsychotic dosage expressed as chlorpromazine equivalence, and did not differ between patients on (n = 7) and off (n = 6) benzodiazepines (Clark et al. 2001). Whilst such post-hoc analyses indicate that the observed attentional deficits cannot be attributed wholly to medication effects, there is evidence from placebo-controlled studies that lithium treatment, for example, does nevertheless have detrimental cognitive effects on memory and psychomotor speed (Honig et al. 1999; Judd et al. 1977). Well-controlled studies addressing the effects of bipolar medications on sustained attention are lacking, and would be a welcome addition to the field.

Selectivity of sustained attention deficit to bipolar disorder

CPT deficits have been reliably demonstrated in schizophrenia (Cornblatt and Keilp 1994; Nuechterlein et al. 1992), and have also been shown with less consistency in acute unipolar depression (Hart et al. 1998; van den Bosch et al. 1996 but not Nelson et al. 1998). However, the state-trait profile of sustained attention deficits in bipolar disorder differentiates it from these other conditions. In schizophrenia, acute symptom fluctuations contribute minimally to the degree of CPT impairment (Liu et al. 2002; Nuechterlein et al. 1992), and treatment with antipsychotic medication does not improve CPT performance, despite considerable symptom improvement (Liu et al. 2000). These findings indicate that CPT deficit may be a stable vulnerability marker in schizophrenia, and this is further supported by evidence of CPT impairments in subjects at high risk for schizophrenia, including unaffected first-degree relatives of schizophrenic patients (Chen et al. 1998; Laurent et al. 1999) and subjects with schizotypal personalities (Grove et al. 1991; Lenzenweger et al. 1991).

In unipolar depression, in contrast, CPT performance appears to recover fully between episodes. Liu et al. (2002) showed intact performance on the degraded stimulus CPT in 22 outpatients with non-psychotic major depression. This group had a mean HAM-D of 5.8, indicating that they were mostly remitted. Similarly, Cornblatt et al. (1989) showed intact performance on a CPT in a group of 17 inpatients and outpatients with depressive disorders. Symptom ratings were not reported, but given that the inpatients in this study had been hospitalised, on average, for more than one month, it seems likely that their symptoms were in partial remission. Using the RVIP, we also found sustained attention in the range of healthy controls in 15 fully-remitted unipolar outpatients with a history of at least two major depressive episodes (mean HAM-D score of 2.1) (Clark and Goodwin, unpublished data). It could be argued that in each of these studies, the unipolar patients had less chronic illnesses (e. g. fewer hospitalisations and later illness onset) compared to the bipolar groups, and therefore that persisting sustained attention deficits could be apparent in more severe recurrent unipolar depression or geriatric depression (cf. Beats et al. 1996; Paradiso et al. 1997). However, given that CPT impairments in bipolar disorder have been shown from first episode, the state-trait profile remains qualitatively distinct from unipolar depression.

Cognitive and physiological mechanisms of sustained attention deficits

CPTs typically place demands on working memory, in order to hold in mind the target sequence(s) to which one is attending. Working memory deficits in bipolar disorder have been emphasised by Thompson et al. (2001), and may confound a deficit in sustained attention. To examine whether sustained attention deficits represent a working memory deficit 'in disguise', we designed a novel CPT that placed minimal demands on working memory. Based on the Mackworth Clock Task (Mackworth 1948), subjects attended to a dot moving in a circular motion, through 60 points as if it were the second hand on a clock face. They were asked to respond if the dot "missed a beat", i. e. jumped two positions in a single movement. This is a straightforward instruction that does not require continuous checking against the target 'template' or updating of working memory, contrasting with the AX-CPT and RVIP. Nineteen patients in the euthymic phase of bipolar disorder were impaired on this task relative to matched controls (Harmer et al. 2002). Furthermore, in a second condition placing a much higher demand on working memory, the euthymic patients were actually unimpaired relative to controls (Harmer et al. 2002). This study demonstrated that sustained attention deficit in bipolar disorder is not confounded by working memory processes.

Sustained attention impairment can be decomposed at a cognitive level in a number of other ways. It seems unlikely that CPT impairment in the euthymic phase reflects reduced target discriminability, because Swann et al. (2003) demonstrated that increased responding to stimuli resembling target strings was only increased during the manic phase of bipolar disorder. A further possibility is that patients with bipolar disorder suffer from disrupted processing of transient visual stimuli. MacQueen et al. (2001) found that euthymic bipolars showed disrupted performance on the visual backwards masking (VBM) paradigm, but one would expect such deficits to generalise across a range of visually-based cognitive tasks. The association between VBM impairments and sustained attention deficit has not been examined.

Why else might euthymic bipolars fail to detect targets on a CPT? Two further possibilities, yet to be thoroughly tested, are that euthymic patients are more prone to distraction from task-irrelevant stimuli, or show reduced levels of arousal. Both alternatives are compatible with the increased vigilance decrement on the RVIP, shown by Clark et al. (2002). Crucially, however, these two explanations generate contrasting hypotheses on how euthymic patients would respond to environmental stress during CPT performance. Mild stressors such as bursts of auditory noise would increase arousal, but at the same time increase distraction from the task (e. g. Hockey 1970).

At a physiological level, sustained responding to unpredictable visual stimuli has been reliably linked to the ascending coeruleo-cortical noradrenaline (NA) projection. Lesions of the ascending noradrenergic bundle impaired target detection on the 5-choice serial reaction time task, an analogue of the CPT for use in rats (Carli et al. 1983). In human subjects, administration of the mixed α_1/α_2 agonist clonidine impaired target detection

on the RVIP (Coull et al. 1995) and increased attentional lapses on a selective attention task (Smith and Nutt 1996). Although an agonist, at the low doses used in human studies, clonidine has an inhibitory action through preferential presynaptic effects dampening locus coeruleus firing and NA release (Freeman and Aghajanian 1984). An elegant series of electrophysiological studies by Aston-Jones and colleagues (Aston-Jones et al. 1999 for review) demonstrated both phasic and tonic contributions of locus coeruleus NA neurons to sustained attention performance. At low levels of tonic activity, the monkeys were drowsy, inattentive and performed poorly, whilst if tonic activity was too high, the monkeys were distractible. This profile of impairment at high and low levels of activity indicates that the relationship between noradrenaline and sustained attention adheres to an inverted-U model.

Administration of the selective α_2 agonist guanfacine to children with ADHD improved CPT performance (Scahill et al. 2001). Similar challenge studies in bipolar disorder, using noradrenaline-enhancers such as guanfacine or reboxetine, provide the direct way to test whether sustained attention deficit is linked to trait noradrenaline disruption, and whether this disruption is associated with under- or over-activity. However, other neurotransmitter systems contribute profoundly to sustained attention as well. Acetylcholine is known to have a critical role in the regulation of cortical arousal, and nicotine, for example, has been shown to improve sustained attention in healthy controls (Koelega 1993) and in patients with Alzheimer's disease (Sahakian et al. 1989). The dopamine and 5-HT systems also modulate response *vigour* on sustained attention tasks, manifested by response speed and the rate of false responding (Harrison et al. 1997; Riekkinen et al. 1998). As discussed above, an increased rate of false responding is seen in the manic state, consistent with hyper-dopaminergic models of mania (Jacobs and Silverstone 1986). Intravenous amphetamine administration models the manic state in healthy subjects, and increases the rate of false responding on the RVIP task. This effect is attenuated by prior administration of a tyrosine-free drink that depletes brain levels of the dopamine precursor (McTavish et al. 2001). The tyrosine depletion manipulation is also effective in temporarily reducing YMRS ratings in manic inpatients (McTavish et al. 2001). Dissection of the sustained attention deficit during the acute and remitted phases of bipolar disorder will therefore require examination of multiple neurotransmitter systems, and it seems unlikely that an abnormality in sustained attention will be underpinned by dysfunction of a single neurochemical system.

In conclusion, continuous performance measures of sustained attention reliably detect cognitive dysfunction in bipolar disorder. A deficit in target detection has been demonstrated in remitted, euthymic patients, who did not show the range of impairments variously described in other samples. The deficit cannot be attributed to residual affective symptoms. There are preliminary indications that this deficit is present from the first bipolar episode, but the deficit also becomes more severe with progression of the disorder, particularly linked to the number (or duration) of acute episodes. During the manic phase of the illness, target detection deficits are exacerbated, and the rate of false responding increases. This profile, of trait impairment combined with state modulation, has been called a 'mediating vulnerability factor' (Nuechterlein et al. 1992). This is perhaps the most interesting profile of cognitive deficit in psychiatric illness, providing a link between aetiological factors and the processes that trigger and exacerbate symptoms during acute episodes. Sustained attention deficit may be related to the distractibility, impulsive behaviour, and increased levels of arousal that characterise the manic episodes, but may also be related to the occupational and social difficulties that are now understood to persist through remission. Characterisation of the sustained attention deficit at a neurochemical level may indicate novel pharmacological interventions for both the acute and euthymic phases of bipolar disorder.

References

1. Addington J, Addington D (1997) Attentional vulnerability indicators in schizophrenia and bipolar disorder. Schizophr Res 23: 197–204
2. Albus M, Hubmann W, Wahlheim C, Sobizack N, Franz U, Mohr F (1996) Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. Acta Psychiatr Scand 94:87–93
3. Altshuler LL (1993) Bipolar disorder: are repeated episodes associated with neuroanatomic and cognitive changes? Biol Psychiatry 33:563–565
4. Aston-Jones G, Rajkowski J, Cohen J (1999) Role of locus coeruleus in attention and behavioral flexibility. Biol Psychiatry 46:1309–1320
5. Bearden CE, Hoffman KM, Cannon TD (2001) The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. Bipolar Disord 3:106–150
6. Beats BC, Sahakian BJ, Levy R (1996) Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. Psychol Med 26:591–603
7. Braver TS, Cohen JD, Barch DM (2002) The role of prefrontal cortex in normal and disordered cognitive control: a cognitive neuroscience perspective. In: Stuss DT, Knight RT (eds) Principles of Frontal Lobe Function. OUP, Oxford
8. Carli M, Robbins TW, Evenden JL, Everitt BJ (1983) Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav Brain Res 9:361–380
9. Cavanagh JT, Van Beck M, Muir W, Blackwood DH (2002) Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. Br J Psychiatry 180:320–326
10. Chen WJ, Liu SK, Chang CJ, Lien YJ, Chang YH, Hwu HG (1998) Sustained attention deficit and schizotypal personality features in nonpsychotic relatives of schizophrenic patients. Am J Psychiatry 155:1214–1220
11. Clark L, Iversen SD, Goodwin GM (2001) A neuropsychological investigation of prefrontal cortex involvement in acute mania. Am J Psychiatry 158:1605–1611
12. Clark L, Iversen SD, Goodwin GM (2002) Sustained attention deficit in bipolar disorder. Br J Psychiatry 180:313–319

13. Cornblatt BA, Keilp JG (1994) Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophr Bull 20:31–46
14. Cornblatt BA, Lenzenweger MF, Erlenmeyer-Kimling L (1989) The continuous performance test, identical pairs version: II. Contrasting attentional profiles in schizophrenic and depressed patients. Psychiatry Res 29:65–85
15. Coull JT, Middleton HC, Robbins TW, Sahakian BJ (1995) Clonidine and diazepam have differential effects on tests of attention and learning. Psychopharmacology 120:322–332
16. Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. Ann Rev Neurosci 18:193–222
17. Dickerson FB, Sommerville J, Origoni AE, Ringel NB, Parente F (2001) Outpatients with schizophrenia and bipolar I disorder: Do they differ in their cognitive and social functioning? Psychiatry Res 102:21–27
18. Dion GL, Tohen M, Anthony WA, Waternaux CS (1988) Symptoms and functioning of patients with bipolar disorder six months after hospitalization. Hosp Community Psychiatry 39: 652–657
19. Dougherty DM (1999) IMT/DMT Immediate Memory Task and Delayed Memory Task: a research tool for studying attention and memory processes. Houston, TX, University of Texas Health Sciences Centre
20. Elvevag B, Weinberger DR, Suter JC, Goldberg TE (2000) Continuous performance test and schizophrenia: a test of stimulus-response compatibility, working memory, response readiness, or none of the above? Am J Psychiatry 157:772–780
21. Ferrier IN, Stanton BR, Kelly TP, Scott J (1999) Neuropsychological function in euthymic patients with bipolar disorder. Br J Psychiatry 175:246–251
22. Freeman JE, Aghajanian GK (1984) Idazoxan selectively antagonises alpha-2 adrenoceptors on rat central neurons. Eur J Pharmacology 105:265–272
23. Grove WM, Lebow BS, Clementz BA, Cerri A, Medus C, Iacono WG (1991) Familial prevalence and coaggregation of schizotypy indicators: a multitrait family study. J Abnorm Psychol 100: 115–121
24. Harmer CJ, Clark L, Grayson L, Goodwin GM (2002) Sustained attention deficit in bipolar disorder is not a working memory impairment in disguise. Neuropsychologia 40:1586–1590
25. Harrison AA, Everitt BJ, Robbins TW (1997) Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology 133:329–342
26. Hart RP, Wade JB, Calabrese VP, Colenda CC (1998) Vigilance performance in Parkinson's disease and depression. J Clin Exp Neuropsychol 20:111–117
27. Hockey G (1970) Effect of loud noise on attentional selectivity. Quart J Exp Psychol 22:28–36
28. Honig A, Arts B, Ponds R, Riedel WJ (1999) Lithium induced cognitive side-effects in bipolar disorder: a qualitative analysis and implications for daily practice. Int Clin Psychopharm 14:167–171
29. Jacobs D, Silverstone T (1986) Dextroamphetamine-induced arousal in human subjects as a model for mania. Psychol Med 16: 323–329
30. Judd LL, Hubbard B, Janowsky DS, Huey LY, Takahashi KI (1977) The effect of lithium carbonate on the cognitive functions of normal subjects. Arch Gen Psychiatry 34:355–357
31. Kessing LV (1998) Cognitive impairment in the euthymic phase of affective disorder. Psychol Med 28:1027–1038
32. Koelega HS (1993) Stimulant drugs and vigilance performance: a review. Psychopharmacology 111:1–16
33. Laurent A, Saoud M, Bougerol T, d'Amato T, Anchisi AM, Biloa-Tang M, Dalery J, Rochet T (1999) Attentional deficits in patients with schizophrenia and in their non-psychotic first-degree relatives. Psychiatry Res 89:147–159
34. Lenzenweger MF, Cornblatt BA, Putnick M (1991) Schizotypy and sustained attention. J Abnorm Psychol 100:84–89
35. Liu SK, Chen WJ, Chang CJ, Lin HN (2000) Effects of atypical neuroleptics on sustained attention deficits in schizophrenia: a trial of risperidone versus haloperidol. Neuropsychopharmacology 22:311–319
36. Liu SK, Chiu CH, Chang CJ, Hwang TJ, Hwu HG, Chen WJ (2002) Deficits in sustained attention in schizophrenia and affective disorders: stable versus state-dependent markers. Am J Psychiatry 159:975–982
37. Mackworth NH (1948) The breakdown of vigilance during prolonged visual search. Quart J Exp Psychol 1:6–21
38. MacQueen GM, Young LT, Galway TM, Joffe RT (2001) Backward masking task performance in stable, euthymic out-patients with bipolar disorder. Psychol Med 31:1269–1277
39. Manly T, Robertson IH (1997) Sustained attention and the frontal lobes. In: Rabbitt P (ed) Methodology of frontal and executive function. Psychology Press, Hove, UK, pp 135–150
40. Martinez-Aran A, Vieta E, Colom F, Reinares M, Benabarre A, Gasto C, Salamero M (2000) Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. Psychother Psychosom 69:2–18
41. McTavish SF, McPherson MH, Harmer CJ, Clark L, Sharp T, Goodwin GM, Cowen PJ (2001) Antidopaminergic effects of dietary tyrosine depletion in healthy subjects and patients with manic illness. Br J Psychiatry 179:356–360
42. Murphy FC, Sahakian BJ (2001) Neuropsychology of bipolar disorder. Br J Psychiatry Suppl 41:120–127
43. Nelson EB, Sax KW, Strakowski SM (1998) Attentional performance in patients with psychotic and nonpsychotic major depression and schizophrenia. Am J Psychiatry 155:137–139
44. Nuechterlein KH, Asarnow RF (1993) Degraded stimulus continuous performance test. Los Angeles, CA, UCLA Department of Psychiatry
45. Nuechterlein KH, Dawson ME, Gitlin M, Ventura J, Goldstein MJ, Snyder KS, Yee CM, Mintz J (1992) Developmental Processes in Schizophrenic Disorders: longitudinal studies of vulnerability and stress. Schizophr Bull 18:387–425
46. Paradiso S, Lamberty GJ, Garvey MJ, Robinson RG (1997) Cognitive impairment in the euthymic phase of chronic unipolar depression. J Nerv Ment Dis 185:748–754
47. Parasuraman R (1984) The psychobiology of sustained attention. In: Warm JS (ed) Sustained Attention in Human Performance. Wiley & Sons, London, UK, pp 61–101
48. Parasuraman R, Warm JS, See JE (1998) Brain systems of vigilance. In: Parasuraman R (ed) The attentional brain. MIT Press, Cambridge, MA, pp 221–256
49. Posner MI, Petersen SE (1990) The attention system of the human brain. Annu Rev Neurosci 13:25–42
50. Quraishi S, Frangou S (2002) Neuropsychology of bipolar disorder: a review. J Affect Disord 72:209–226
51. Riekkinen M, Kejonen K, Jakala P, Soininen H, Riekkinen P Jr (1998) Reduction of noradrenaline impairs attention and dopamine depletion slows responses in Parkinson's disease. Eur J Neurosci 10:1429–1435
52. Robbins TW (1998) Arousal and attention: psychopharmacological and neuropsychological studies in experimental animals. In: Parasuraman R (ed) The attentional brain. MIT Press, Cambridge, MA, pp 189–219
53. Rosvold HE, Mirsky AF, Sarason I, Bransome ED, Beck LH (1956) A continuous performance test of brain damage. J Consult Psychol 20:343–350
54. Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ (2000) Cognitive impairment in remission in bipolar affective disorder. Psychol Med 30:1025–1036
55. Rund BR, Orbeck AL, Landro NI (1992) Vigilance deficits in schizophrenics and affectively disturbed patients. Acta Psychiatr Scand 86:207–212
56. Sahakian B, Jones G, Levy R, Gray J, Warburton D (1989) The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. Br J Psychiatry 154:797–800
57. Sax KW, Strakowski SM, Keck PE Jr, McElroy SL, West SA, Stanton SP (1998) Symptom correlates of attentional improvement following hospitalization for a first episode of affective psychosis. Biol Psychiatry 44:784–786

58. Sax KW, Strakowski SM, Zimmerman ME, DelBello MP, Keck PE Jr, Hawkins JM (1999) Frontosubcortical neuroanatomy and the continuous performance test in mania. Am J Psychiatry 156: 139–141
59. Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, Arnsten AF, Cohen DJ, Leckman JF (2001) A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry 158:1067–1074
60. Scott J (1995) Psychotherapy for bipolar disorder. Br J Psychiatry 167:581–588
61. Seidman LJ, Kremen WS, Koren D, Faraone SV, Goldstein JM, Tsuang MT (2002) A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. Schizophr Res 53:31–44
62. Smith A, Nutt D (1996) Noradrenaline and attention lapses. Nature 380:291
63. Swann AC, Pazzaglia P, Nicholls A, Dougherty DM, Moeller FG (2003) Impulsivity and phase of illness in bipolar disorder. J Aff Disord 73:105–111
64. Thompson JM, Gray JM, Wilkinson BS, Hughes JM, Del-Estal D, Watson S, Ferrier IN, Young AH (2001) Impaired working memory monitoring on the Self-Ordered Pointing Task in euthymic bipolar patients. J Psychopharmacology 15(suppl.):A67
65. van den Bosch RJ, Rombouts RP, van Asma MJ (1996) What determines continuous performance task performance? Schizophr Bull 22:643–651
66. van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W (1998) Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. Arch Gen Psychiatry 55:41–46
67. Wilder-Willis KE, Sax KW, Rosenberg HL, Fleck DE, Shear PK, Strakowski SM (2001) Persistent attentional dysfunction in remitted bipolar disorder. Bipolar Disord 3:58–62
68. Zubieta JK, Huguelet P, O'Neil RL, Giordani BJ (2001) Cognitive function in euthymic bipolar I disorder. Psychiatry Res 102:9–20