# Sustained Attention-Deficit Confirmed in Euthymic Bipolar Disorder but Not in First-Degree Relatives of Bipolar Patients or Euthymic Unipolar Depression

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***Background:*** *Cognitive dysfunction persists in the euthymic phase of bipolar disorder and may provide a marker of underlying neuropathology and disease vulnerability. This study aimed to replicate a deficit in sustained attention in euthymic bipolar patients and investigate sustained attention in first-degree relatives of bipolar probands and in remitted patients with major depressive disorder.*

***Methods:*** *The rapid visual information processing (RVIP) task was used to measure sustained attention in 15 euthymic patients with bipolar disorder and 15 control subjects in experiment 1 and in 27 first-degree relatives of bipolar probands, 15 remitted patients with major depressive disorder, and 46 control subjects in experiment 2.*

***Results:*** *Sustained attention deficit was confirmed in the euthymic bipolar patients in experiment 1, but the deficit was not statistically significant in remitted major depressed patients or in the relatives of bipolar probands.*

***Conclusions:*** *A deficit of sustained attention is not present in patients with recurrent major depression tested during remission nor is it discriminable in the first-degree relatives of bipolar probands. Thus, the confirmed abnormality in euthymic bipolar patients may be acquired as a consequence of bipolar illness. However, future studies of relatives will require larger sample sizes to exclude or utilize small genetic effects.*

**Key Words:** Mood disorders, mania, schizophrenia, vigilance, executive function, neuropsychology

The term endophenotype is used in psychiatric genetics to refer to an illness marker that is directly associated with underlying vulnerability distinct from the disease phenotype itself (Cornblatt and Malhotra 2001). The identification of an endophenotype for bipolar disorder would facilitate early detection and treatment and provide a marker for genetic research (Almasy and Blangero 2001). The present study investigates deficits in sustained attention as an endophenotype for bipolar disorder. Sustained attention (or vigilance) can be quantified in neuropsychological assessment using continuous performance tests (CPTs). There are several CPT variants (see Rosvold et al 1956; Swann et al 2003; Wesnes and Warburton 1984), but in all tasks a continuous stream of visual stimuli (e.g., numbers) must be monitored for infrequent and nonsalient targets (e.g., a prespecified number sequence). Continuous performance tests last for several minutes to assess the maintenance of focused attention. Optimal performance requires an adequate level of arousal, combined with an element of executive control to resist distraction and inhibit responses to stimuli resembling targets (Manly and Robertson 1997; Parasuraman et al 1998).

Impaired sustained attention is a robust feature of the manic (Clark et al 2001; Sax et al 1999) and depressive state (Hart et al 1998; Rund et al 1992), and sustained attention deficit persists during the euthymic phase of bipolar disorder (Clark et al 2002; Harmer et al 2002; Liu et al 2002; Wilder-Willis et al 2001). The deficit is not attributable to working memory demands (Harmer et al 2002) and cannot be explained by residual affective symptomatology (Clark et al 2002), although the degree of impairment may be exacerbated during acute manic episodes (Clark et al 2001; Swann et al 2003). Although the extent of the impairment correlated with both the number of bipolar affective episodes and the duration of illness—compatible with an acquired trait—it was also present in a subset of young bipolar patients with short illness durations (Clark et al 2002).

Bipolar disorder is highly heritable, with family members at 10-fold to 20-fold increased risk of developing a bipolar diagnosis over population rates (Craddock and Jones 1999; Gershon et al 1982). Neuropsychological abnormalities have considerable promise as endophenotypic markers for psychiatric disorders because they are quantitative, they have moderate heritability within the normal population (Dougherty et al 2003), and they can be extended to animal models of the disorder (Glahn et al 2004). Previous studies using neuropsychological testing in the first-degree relatives of patients with schizophrenia have typically demonstrated a profile of neurocognitive deficits similar to schizophrenia, albeit attenuated (Chen et al 1998; Faraone et al 1999; Goldberg et al 2003; Keefe et al 1994). Relatives of patients with affective psychoses have revealed less evidence of impairment (Gilvarry et al 2001; Gourovitch et al 1999; Keri et al 2001; Kremen et al 1998), although sustained attention could be a more sensitive vulnerability marker that has been overlooked to date (Glahn et al 2004).

In the present study, we sought, first, to replicate our previous observation (Clark et al 2002; Harmer et al 2002) of sustained attention deficit on the rapid visual information processing (RVIP) task in an entirely independent sample of bipolar patients tested in the euthymic state and, second, to examine whether a similar deficit was also present in the unaffected first-degree relatives of patients with bipolar I disorder (REL-BPD) and in remitted patients with recurrent major depressive disorder (MDD).

## Methods and Materials

### Experiment 1

**Subjects.** Fifteen patients with a DSM-IV diagnosis of bipolar disorder (14 bipolar I, 1 bipolar II) were recruited from Charing

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Cross Hospital and from advertisements placed in the Manic Depression Fellowship newsletter. The research protocol was approved by the Hammersmith and Queen Charlotte's & Chelsea Hospitals Research Ethics Committee. After complete description of the study, written informed consent was obtained from all subjects. The patients ranged in age from 22 to 63 years (mean 37.8, SD 14.6), with a National Adult Reading Test (NART)-estimated verbal intelligence quotient (IQ) (Nelson and Willison 1991) of 115.7 (SD 5.1). All patients were euthymic at the time of testing, as defined by a rating of <9 on the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and <9 on the Young Mania Rating Scale (YMRS) (Young et al 1978). Most patients were medicated with mood stabilizers (in five cases with an adjunctive antidepressant): lithium (four), carbamazepine (two), sodium valproate (three), and a combination of lithium and valproate (two). Three patients were receiving an antipsychotic medication, and three patients were unmedicated. Two subjects had received electroconvulsive therapy in the past (at least 1 year prior to testing). None of the subjects had current psychiatric comorbidity or were currently abusing drugs or alcohol (assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID]) (First et al 1996). Four subjects met criteria for lifetime alcohol/substance abuse (two polydrug, one alcohol, one cannabis).

Fifteen healthy comparison subjects were recruited by newspaper advertisement, with a mean age of 38.0 (SD 11.0) and NART-estimated verbal IQ of 115.4 (SD 6.5). The control subjects had no psychiatric history, including lifetime drug or alcohol abuse (assessed using the SCID), and had no first-degree relatives with a psychiatric history (assessed by self-report). Two subjects were taking nonpsychoactive medications on the day of testing (paracetamol and a bladder control medication).

**Procedure.** Subjects were administered the rapid visual information processing task (see Coull et al 1995; Wesnes and Warburton 1984) following mood assessment with the HDRS and YMRS. The RVIP is a continuous performance test lasting 7 minutes where subjects are required to monitor a continuous stream of digits, presented at the rate of 100 digits per minute, for prespecified digit strings (e.g., 3-5-7, in consecutive order). The digit strings are displayed to the right side of the stimuli throughout the task, to reduce the demand for working memory. Subjects respond to target strings by pressing a button box linked to the parallel port. Correct detections ("hits") of target strings can be registered during the last digit of a sequence or in the subsequent 1800 milliseconds. The average latency of correct detections and the number of commission errors (false alarms to nontarget) are also assessed. In analysis, correct detections and commission errors are converted to the signal detection variables target sensitivity (A') and response bias (B") (Green and Swets 1966; Grier 1971). Target sensitivity is an index of perceptual discriminability of target stimuli from noise (from 0 to 1), whereas response bias indicates the tendency to respond regardless of whether a target is present (from −1 to +1). In the RVIP task used in experiment 1, there were four target sequences with eight targets presented every minute. This is a more difficult version than the task used in experiment 2 (the task was an adaptation for functional imaging work designed to maximize sensitivity in small groups).

### Experiment 2

**Subjects.** The study was approved by the Oxfordshire Psychiatric Research Ethics Committee. After complete description of the study to the subjects, written informed consent was obtained. Twenty-seven first-degree relatives of 18 patients with a DSM-IV diagnosis of bipolar I disorder were recruited after screening with the SCID. Exclusion criterion were a current axis I diagnosis or a previous hospitalization for psychiatric illness. Several subjects reported previous episodes of affective disturbance: major depressive episode (five subjects), bipolar II disorder (one subject), hypomanic episode (one subject), subclinical depressive episodes (four subjects). These subjects were included in the study to avoid selection of a "super-normal" group. Sixteen subjects reported no psychiatric history. The final group consisted of 10 parents, 12 siblings, and 5 offspring of bipolar probands, resulting in a broad age range of 17 to 68 years.

Fifteen subjects with a history of at least two major depressive episodes, confirmed using the SCID, were recruited from the outpatient clinic in Oxford. These subjects had no personal history of hypomanic or manic episodes, no family history of bipolar disorder or schizophrenia, and were euthymic at the time testing (defined as <9 on the HDRS). Six subjects were currently receiving antidepressant medication: selective serotonin reuptake inhibitors (SSRIs) (2 patients), tricyclics (3 patients), and a combination of an SSRI and selective noradrenergic reuptake inhibitor (SNRI) (1 patient).

A control sample of 46 subjects was used for normative comparison. Control subjects had no personal history of psychiatric disorder (assessed using the SCID) or psychiatric hospitalization and no family history of psychosis (assessed by self-report at interview). Control subjects were not receiving medication around the time of testing.

**Procedure.** Rapid visual information processing was identical to the task in experiment 1, with the exception that there were three target sequences, with nine targets presented every minute. Results are thus not directly comparable between experiments 1 and 2. Rapid visual information processing was one of a small battery of tests presented in a fixed order.

### Statistical Analysis

Demographic and cognitive data were analyzed using one-way analysis of variance (ANOVA) with two-tailed statistics, threshold $p < .05$. Performance indices from the RVIP task were target sensitivity, response bias, and average latency on correct responses. Accuracy (percentage of targets detected) is also displayed in Tables 2 and 4 to indicate performance in relation to ceiling (CPTs can be susceptible to ceiling effects which may obscure between-group differences). Target sensitivity was correlated against mood ratings on the HDRS and YMRS and against duration of illness in the euthymic bipolars in experiment 1.

## Results

### Experiment 1

Demographic data for the euthymic cases with bipolar disorder and control subjects are displayed in Table 1. Patients and control subjects were matched in terms of age ($t_{28}$= .042, $p$ = .97), gender (chi-square = 0, $p$ = 1), and NART-estimated verbal IQ ($t_{28}$ = .14, $p$ = .89). Analysis of RVIP performance indicated reduced target sensitivity and slowed response latency in the bipolar group compared with control subjects but no effect on response bias (see Table 2). The deficits in target sensitivity and response latency were not associated with depression ratings on the HDRS (target sensitivity: $r_{15}$ = −.13, $p$ = .64; latency: $r_{15}$ = −.26, $p$ = .36) or mania ratings on the YMRS (target sensitivity: $r_{15}$ = .07, $p$ = .81; latency: $r_{15}$ = −.26, $p$ = .36). Rapid visual information processing deficits were also unrelated to the dura-

**Table 1.** Demographic and Mood Scale Characteristics of the Euthymic Cases with Bipolar Disorder and Control Subjects in Experiment 1 (Mean [SD])

| | Control Subjects | Euthymic Bipolar Disorder |
|---|---|---|
| *N* | 15 | 15 |
| Male:Female | 3:12 | 3:12 |
| Age | 37.8 (14.6) | 38.0 (11.0) |
| NART | 115.7 (5.1) | 115.4 (6.5) |
| HAM-D | – | 3.2 (2.5) |
| YMRS | – | 1.9 (2.5) |
| Duration of Illness (years) | – | 13.3 (9.3) |

NART, National Adult Reading Test; HAM-D, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

tion of illness (target sensitivity: $r_{15} = -.109$, $p = .698$; latency: $r_{15} = .092$, $p = .746$).

### Experiment 2

The three groups were matched for age [$F(2,85) = 1.59$, $p = .211$], years education [$F(2,85) = 1.19$, $p = .310$], and NART-estimated verbal IQ [$F(2,81) = .403$, $p = .670$] (see Table 3). The gender ratio did not differ significantly across groups (chi-square = 2.60, $df = 2$, $p = .273$), but the proportion of female participants was greater in the remitted MDD group. Rapid visual information processing performance is shown in Table 4. Analysis of variance showed no effect of group on target sensitivity [$F(2,85) = 1.27$, $p = .287$], response latency [$F(2,85) = .559$, $p = .574$), or response bias [$F(2,85) = .114$, $p = .892$]. These results were unchanged by inclusion of gender as a covariate. In the groups of relatives and remitted MDD, target sensitivity did not correlate with mood ratings on the HDRS (relatives: $r_{27} = -.05$, $p = .805$; remitted MDD: $r_{15} = -.105$, $p = .711$) or YMRS (relatives: $r_{27} = .168$, $p = .401$; remitted MDD: $r_{15} = -.234$, $p = .401$).

Rapid visual information processing data were available for 13 of the 18 bipolar probands. In a post hoc analysis, these patients were compared with the three groups from experiment 2 who were tested on the same version of the RVIP task. The probands were matched to the three groups in terms of age [$F(3,98) = 1.49$, $p = .222$] and NART-estimated verbal IQ [$F(3,91) = .368$, $p = .776$]. One proband scored 9 (hypomanic) on the YMRS, and a second scored 10 (mildly depressed) on the HDRS; all others were euthymic at testing (scores <9). The one-way ANOVA (4-level) revealed no significant main effect of group in target sensitivity [$F(3,97) = 2.14$, $p = .10$), but a planned comparison revealed reduced target sensitivity in the probands compared with control subjects ($t_{97} = 2.35$, $p = .021$). The difference between the bipolar probands and the relatives was not significant ($t_{97} = 1.11$, $p = .271$) and the difference between the probands and the remitted MDD was not significant ($t_{97} = 1.63$, $p = .106$). This analysis should be treated with caution because of the small number of probands with RVIP data.

## Discussion

The present data replicate our previous observation (Clark et al 2002) of sustained attention deficit in euthymic patients with bipolar disorder in an independent group of patients and with a slightly different continuous performance task. These subjects showed reduced target sensitivity (an index of target detection) and slowed response latencies. There was no alteration in response bias (an index of response tendency) in the euthymic bipolar patients. This contrasts with impulsive responding in acute manic episodes (Clark et al 2001; Swann et al 2003). The sustained attention deficit did not correlate with subclinical ratings of depressive and manic symptoms that commonly persist during periods of remission and can account for cognitive impairment in other domains (Ferrier et al 1999; Clark et al 2002). We have also shown previously that sustained attention deficit during the euthymic phase cannot be explained by the working memory demands that are inherent to many continuous performance measures (Harmer et al 2002). Thus, sustained attention deficit is robustly associated with bipolar disorder and persists during periods of euthymic mood.

There was no statistically discernible impairment in sustained attention in the sample of first-degree relatives of patients with bipolar I disorder, compared with a large sample of age- and education-matched control subjects. Caution is nevertheless required with negative findings. The group of relatives did perform, on average, slightly below the level of the control subjects on the RVIP, and 4 of 27 relatives scored more than two standard deviations below the control group mean (compared with 1 of 46 control subjects) and reaction times tended to be slower. The effect size (d) for our comparison was .38—a small-to-medium effect in the boundaries set by Cohen (1988). To confirm a statistically significant difference at this effect size, future case-control studies should aim to recruit ~115 subjects per group (power .81, alpha = .05). If sustained attention deficit is to represent a useful cognitive endophenotype for bipolar disorder, this calculation should guide sample sizes. Selection criteria may also dictate the level of vulnerability in a sample of first-degree relatives. Excluding all relatives with any psychiatric history risks selecting a "super-normal" group, which we attempted to minimize by including some relatives with personal histories of mild affective disturbance. In addition, selection of unrepresentative, higher-functioning bipolar probands could produce a false-negative in first-degree relatives. A significant RVIP deficit was apparent in the bipolar probands of our group of relatives, so this is unlikely to be a major factor here.

Performance was also at the level of control subjects in a group of remitted outpatients with recurrent major depressive disorder. The effect size for this case-control comparison was .11, a small effect in the Cohen boundaries, which would require over 1200 subjects per group to achieve a power of .80 (alpha .05) in future research. This indicates that the state-trait profile of sustained attention deficit shows some specificity to bipolar disorder. Impaired performance on CPTs has been demonstrated during acute depressive episodes (Hart et al 1998; van den Bosch et al 1996) but appears to recover fully in remission. This is consistent with the data of Liu et al (2002), showing intact sustained attention in a group of MDD outpatients with a mean score on the Hamilton Depression Scale of 5.8 (a score <9 indicates euthymia). The state-trait profile also contrasts with

**Table 2.** Experiment 1: Rapid Visual Information Processing (RVIP) Performance (Mean [SD]) in the Euthymic Cases with Bipolar Disorder and Matched Controls Subjects

| | Control Subjects | Euthymic Bipolar Disorder | $F_{(1,28)}$ |
|---|---|---|---|
| Target Sensitivity | .89 (.035) | .85 (.046) | 8.66, $p = .006$ |
| Response Bias | .97 (.029) | .93 (.102) | 2.67, $p = .11$ |
| Response Latency (ms) | 424 (52) | 518 (130) | 6.88, $p = .014$ |
| Accuracy (%) | 57.3 (13.7) | 42.3 (16.1) | N/A |

N/A, not applicable.

**Table 3.** Demographic and Mood Scale Characteristics of the First-Degree Relatives of Bipolar I Patients, Patients with Remitted Major Depressive Disorder, and Control Subjects in Experiment 2 (Mean [SD])

| | Control Subjects | Bipolar Relatives | Remitted MDD | Bipolar Probands[a] |
|---|---|---|---|---|
| *N* | 46 | 27 | 15 | 13 |
| Male: Female | 23:23 | 13:14 | 4:11 | 7:6 |
| Age | 39.2 (12.2) | 43.2 (14.4) | 45.2 (10.9) | 37.3 (11.5) |
| NART | 117.9 (5.3) | 118.5 (4.5) | 117.3 (7.5) | 119.1 (5.3) |
| Years Education | 15.1 (2.9) | 14.4 (2.6) | 13.9 (2.9) | 14.9 (1.6) |
| HAM-D | – | 1.2 (1.9) | 2.1 (2.9) | 3.9 (2.8) |
| YMRS | – | .4 (1.1) | .9 (1.1) | 1.6 (2.5) |

MDD, major depressive disorder; NART, National Adult Reading Test; HAM-D, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

[a]RVIP data was available for 13 of the 18 probands with bipolar 1 disorder.

schizophrenia, where sustained attention deficit is relatively unaffected by clinical state (Nuechterlein et al 1992). For example, acute symptom improvements as a result of neuroleptic treatment confer minimal benefit to CPT performance in schizophrenia (Liu et al 2000, 2002). The sustained attention profile in bipolar disorder indicates a state-modulated trait marker (Clark and Goodwin 2004). A cognitive marker with this profile may provide novel insight into the interaction between underlying neuropathology in bipolar disorder and brain mechanisms responsible for acute symptom fluctuations.

A number of caveats and limitations should be mentioned. First, a proportion of patients in the euthymic bipolar group (experiment 1) and remitted MDD group (experiment 2) were taking psychiatric medications at the time of testing, and these treatments may have influenced RVIP performance. The long-term neuropsychological effects of prophylactic treatment in bipolar disorder are poorly understood, but there is some evidence for adverse effects of lithium on psychomotor speed and memory (Honig et al 1999; (Judd et al 1977). In our previous study, the RVIP deficit did not differ between euthymic bipolar patients on ($n$ = 19) and off ($n$ = 11) lithium and remained significant in those patients off lithium compared with control subjects (Clark et al 2002). It also seems unlikely that the SSRI treatment in 6 of 15 remitted MDD subjects effectively masked any sustained attention deficit in this group (target detection: on medication, mean = 71% [SD 12]; off medication, mean = 68% [SD 18]). Second, the proportion of subjects receiving medication was smaller in the remitted MDD group compared with the euthymic bipolar group in experiment 1 (6 of 15 versus 12 of 15, respectively). It is arguable that the remitted MDD group may have had less severe or chronic illnesses than the bipolar group and therefore that sustained attention deficit may be apparent in more chronic cases with recurrent MDD (e.g., Paradiso et al 1997). Given previous data that sustained attention deficits are apparent in bipolar disorder patients even with short illness durations (Clark et al 2002), this would still indicate a qualitative difference between the state-trait profile of bipolar and unipolar affective disorders. Third, the lack of association between RVIP performance and mood ratings must be regarded as preliminary because of the restricted range of mood scores. Previous studies have shown that subclinical scores on the HDRS and YMRS can contribute to cognitive impairment (Clark et al 2002; Ferrier et al 1999), but future research may benefit from more sensitive measures of residual mood symptoms. Fourth, the different variants of the RVIP tasks used in experiments 1 and 2 preclude direct comparison across the two experiments. Hence, it might appear from Tables 2 and 4 that control subjects performed more poorly in experiment 1, but this RVIP variant had a higher working memory load. This feature may also explain why the bipolar cases in experiment 1 showed a more significant deficit ($p$ = .006) than the bipolar probands in experiment 2 ($p$ = .021).

**Table 4.** Sustained Attention Performance on the Rapid Visual Information Processing (RVIP) Task in the First-Degree Relatives of Bipolar Patients, Patients with Remitted Major Depressive Disorder, and Control Subjects in Experiment 2 (Mean [SD])

| | Control Subjects | Relatives | Euthymic MDD | Bipolar Probands |
|---|---|---|---|---|
| Target Sensitivity | .93 (.043) | .91 (.056) | .92 (.040) | .89 (.067) |
| Response Bias | .96 (.046) | .96 (.058) | .96 (.034) | .96 (.079) |
| Response Latency (ms) | 494 (82.7) | 516 (99.2) | 497 (95.0) | 525 (45.8) |
| Accuracy (%) | 71.3 (17.5) | 64.0 (22.0) | 69.4 (15.6) | 59.6 (17.7) |

Available data for 13 (of 18) bipolar probands are included for comparison.

Investigation of first-degree relatives in the search for psychiatric endophenotypes is limited by a number of factors. Primarily, we perhaps should not expect all relatives to display an endophenotypic marker, only a subgroup, and the level of genetic variability may vary widely across studies. The relatives group in the present study constituted parents, siblings, and children of affected probands. The average age of the relatives was above the average age of onset for bipolar disorder, and it is therefore unlikely that many subjects would develop bipolar disorder subsequently. By implementing rigorous exclusion criteria for psychiatric history in mature samples, researchers may inadvertently select subjects with genetic resilience rather than genetic risk. To increase the level of genetic vulnerability in high-risk research, further studies could investigate so-called obligate carriers (unaffected relatives with both an affected child and parent) or the parametric influence of familial loading (the number of affected relatives) (Faraone et al 2000). Finally, cognitive impairments in the relatives of bipolar patients may only become apparent under challenge, either using a pharmacological manipulation such as tryptophan depletion (Sobczak et al 2002) or a psychological manipulation such as stress or sleep deprivation (Wehr et al 1982), known to trigger acute episodes in bipolar disorder.

In conclusion, the present study has confirmed the persistent dysfunction of sustained attention in patients with bipolar disorder tested during periods of euthymic mood. Sustained attention deficit was not apparent in the euthymic phase of major depressive disorder. It remains unclear whether the deficit in bipolar patients is present premorbidly, manifests around the time of illness onset, or develops as a consequence of repeated episodes. Examination of

first-degree relatives did not prove sustained attention deficits in the premorbid stage, but they may be present and we have defined the likely power required to detect them. In the present data, there was no correlation between RVIP target detection and the duration of bipolar illness, although this effect may be limited by the small number of patients and has been demonstrated in previous work (Clark et al 2002). Our previous findings (Clark et al 2002) in young adult patients with short illness durations indicate that the initial bipolar episodes may be critical. Sustained attention deficit may assume increasing importance in bipolar disorder in relation to functional outcome and as a neuropsychological mediator between underlying neuropathology and acute symptom fluctuations.

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