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ORIGINAL ARTICLE

Neurocognitive intra-individual variability in mood disorders: effects on attentional response time distributions

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Background. Attentional impairment is a core cognitive feature of major depressive disorder (MDD) and bipolar disorder (BD). However, little is known of the characteristics of response time (RT) distributions from attentional tasks. This is crucial to furthering our understanding of the profile and extent of cognitive intra-individual variability (IIV) in mood disorders.

Method. A computerized sustained attention task was administered to 138 healthy controls and 158 patients with a mood disorder: 86 euthymic BD, 33 depressed BD and 39 medication-free MDD patients. Measures of IIV, including individual standard deviation (*iSD*) and coefficient of variation (*CoV*), were derived for each participant. Ex-Gaussian (and Vincentile) analyses were used to characterize the RT distributions into three components: *mu* and *sigma* (mean and standard deviation of the Gaussian portion of the distribution) and *tau* (the 'slow tail' of the distribution).

Results. Compared with healthy controls, *iSD* was increased significantly in all patient samples. Due to minimal changes in average RT, *CoV* was only increased significantly in BD depressed patients. Ex-Gaussian modelling indicated a significant increase in *tau* in euthymic BD [Cohen's $d = 0.39$, 95% confidence interval (CI) 0.09–0.69, $p = 0.011$], and both *sigma* ($d = 0.57$, 95% CI 0.07–1.05, $p = 0.025$) and *tau* ($d = 1.14$, 95% CI 0.60–1.64, $p < 0.0001$) in depressed BD. The *mu* parameter did not differ from controls.

Conclusions. Increased cognitive variability may be a core feature of mood disorders. This is the first demonstration of differences in attentional RT distribution parameters between MDD and BD, and BD depression and euthymia. These data highlight the utility of applying measures of IIV to characterize neurocognitive variability and the great potential for future application.

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Introduction

Neurocognitive dysfunction is a common feature of mood disorders. Deficits in a range of cognitive processes have been described during symptomatic episodes in major depressive disorder (MDD) (Zakzanis *et al.* 1998; Lee *et al.* 2012; Rock *et al.* 2014) and bipolar disorder (BD) (Rubinsztein *et al.* 2006; Kurtz & Gerraty, 2009; Gallagher *et al.* 2014, 2015), including in medication-free patients (Porter *et al.* 2003; Taylor Tavares *et al.* 2007). There has long been an emphasis on the extent to which such deficits can be observed in clinical remission (Astrup *et al.* 1959; Bratfos & Haug, 1968), with growing consensus that they may be state-independent (Robinson *et al.* 2006; Torres *et al.* 2007; Arts *et al.* 2008; Bora *et al.* 2013; Bourne *et al.* 2013). The further identification – albeit less consistently – of modest dysfunction in the non-affected, first-degree relatives of affected probands (Balanzá-Martínez *et al.* 2008; Bora *et al.* 2009) has resulted in some aspects of neurocognitive dysfunction being put forward as candidate cognitive endophenotypes for mood disorders. Due to a paucity of studies in some areas, there remains debate over the extent to which specific cognitive deficits can be viewed as

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true endophenotypes (i.e. heritable, co-segregating, and found in non-affected family members at a higher rate than in the general population; Gottesman & Gould, 2003) rather than core illness 'traits', emerging consequent to the mood disorder (Glahn *et al.* 2004; Christensen *et al.* 2006; Daban *et al.* 2012).

Impairments in facets of attentional processing have been described in many studies of neurocognitive function in mood disorders (Cohen *et al.* 2001). Deficits have been observed in MDD and BD patients when euthymic (Paelecke-Habermann *et al.* 2005; Torrent *et al.* 2006; Preiss *et al.* 2009; Robinson *et al.* 2013) as well as abnormalities in the activation of underlying neurocircuitry when performing attentional tasks (Strakowski *et al.* 2004; Mullin *et al.* 2012). Following the observation of deficits in first-degree relatives of BD patients, and euthymic recurrent MDD patients, attentional control (cognitive flexibility) has been suggested as a candidate endophenotype for mood disorder in general (but not actual disease phenotypes) (Clark *et al.* 2005*b*). However, one of the most frequently examined aspects of attention in mood disorders has been vigilance (or sustained attention). Performance decrements, which increase with time-on-task, on the degraded stimulus form of the continuous performance test (CPT) in euthymic BD patients have led to the suggestion that alterations in sustained attention may be an endophenotype for BD (Ancín *et al.* 2010). Numerous other studies have demonstrated CPT deficits in BD and MDD patients in symptomatic states (Koetsier *et al.* 2002; Porter *et al.* 2003; Fleck *et al.* 2012; Gallagher *et al.* 2014) and in euthymia (Wilder-Willis *et al.* 2001; Liu *et al.* 2002; Weiland-Fiedler *et al.* 2004; Doyle *et al.* 2005; Thompson *et al.* 2005; Kolur *et al.* 2006). CPT deficits have also been observed in some (Klimes-Dougan *et al.* 2006; Trivedi *et al.* 2008) but not all (Clark *et al.* 2005*a*; Meyer & Blechert, 2005; Jabben *et al.* 2009; Walshe *et al.* 2012) studies in first-degree relatives. A recent study found both behavioural deficits and functional magnetic resonance imaging differences (increased activation in the insula and parts of the cingulate cortex) during a CPT in euthymic BD-I patients and non-affected relatives compared with controls (Sepede *et al.* 2012).

One important consideration in the assessment of attentional processes is in the method of performance measurement. In most CPTs, absolute errors, signal detection indices or mean reaction time (RT) over subcomponents or the overall task are typically used. However, increasingly there is recognition of the need to go beyond such measures and take into account inconsistency of responses or intra-individual variability (IIV). This can be achieved most simply by calculation of the standard deviation of item-by-item RT for each individual (or the individual standard deviation; *iSD*), although as this measure is strongly related to mean RT, the coefficient of variation (*CoV*) is often preferred (Jackson *et al.* 2012) which divides the *iSD* by the corresponding individual's mean RT. Such measures are being increasingly applied in the cognitive ageing literature (Nilsson *et al.* 2014), where it has been reported that IIV indices are better than mean RT in differentiating early neurodegeneration from healthy ageing (Hultsch *et al.* 2002), and are strongly related to broader cognitive function (Bielak *et al.* 2010) and brain white matter integrity (Fjell *et al.* 2011; Jackson *et al.* 2012). However, empirical RT distributions are fundamentally non-normal and tend to be positively skewed and there is growing interest in the utility of mathematical RT modelling to characterize dissociable components of RT distributions (Balota & Yap, 2011).

The ex-Gaussian distribution, a mathematical convolution of a Gaussian (normal) and exponential distribution, produces a good approximation to empirical RT distributions (Schmiedek *et al.* 2007). The ex-Gaussian distribution has three parameters: *mu* and *sigma*, the mean and standard deviation of the Gaussian (normal) component; and *tau*, which determines the exponential component and represents the relative strength of the 'slow-tail' of the distribution (Ratcliff, 1979). As the ex-Gaussian model represents the distribution of RT, it can intuitively be related to 'standard' arithmetic properties, for example, the sum of *mu* and *tau* equals the overall arithmetic mean of the data (Ratcliff, 1979; Heathcote *et al.* 1991). This methodology has been used to model RT from a number of attentional tasks in older adults, for example, demonstrating a clear increase in the *tau* component in mild dementia of the Alzheimer's type compared with controls, which correlated with decreased cerebral white matter (Tse *et al.* 2010; Jackson *et al.* 2012). More generally, RT variability has been linked to white matter integrity across the normal developmental trajectory in healthy children, adolescents and adults: maturation of white matter integrity and connectivity leading to reductions in RT IIV (Fjell *et al.* 2011; Tamnes *et al.* 2012). Given the growing evidence of impaired white matter integrity in MDD and BD patients and those at high-risk (Heng *et al.* 2010; Macritchie *et al.* 2010; Sprooten *et al.* 2011; Henderson *et al.* 2013; Leow *et al.* 2013; Sarrazin *et al.* 2014; Wang *et al.* 2014) there is a clear rationale for applying such analyses to attentional RT data in mood disorder.

Despite the potential utility of these approaches, there are very few data on IIV in mood disorders. Increased variability on the Connors CPT in manic and euthymic patients has been reported (Bora *et al.* 2006), although variability was examined between average blocks of trials rather than individual RT.

One study found a large effect size in the increase in RT *iSD* from a CPT in young BD probands and their unaffected first-degree relatives compared with matched controls (Brotman *et al.* 2009). It has been reported that RT *iSD* from a Go/No-go paradigm was increased in patients with schizophrenia/schizo-affective disorder, but not in those with major depression or borderline personality disorder compared with healthy controls (Kaiser *et al.* 2008). To date there has been no comprehensive assessment of attentional IIV, with full RT modelling, in mood disorders.

The aim of the present study was therefore to examine RT distributions from an attentional CPT in patients with mood disorders, comparing *iSD, CoV* and ex-Gaussian components (*mu, sigma* and *tau*) in patients with BD (euthymia and depression), medication-free depression and healthy control participants. As the ex-Gaussian is a parametric model of an underlying theoretical distribution, Vincentile analysis was also conducted in order to demonstrate convergence across the two techniques (Tse *et al.* 2010). This non-parametric technique directly assesses raw empirical RT distributions and makes no assumptions about an underlying theoretical distribution (by first ordering and then dividing the empirical distribution into a number of equal-sized 'bins' and computing the average RT in each of these bins). It was hypothesized that, overall, the mood disorder groups would show a significantly increased IIV and ex-Gaussian *tau* component (reflecting increased response variability, especially slowing) compared with matched controls.

Method

Individual RT datasets were collated from multiple studies conducted in the Institute of Neuroscience (Academic Psychiatry), Newcastle University which had used the same attentional task (Porter *et al.* 2003; Thompson *et al.* 2005; Macritchie *et al.* 2010; Gallagher *et al.* 2014).

Participants

Patients aged 18–65 years with a diagnosis of BD, confirmed using the Structured Clinical Interview for DSM-IV (SCID; First *et al.* 1995), were recruited from secondary and tertiary care services in the North East of England. All were out-patients and either currently in a depressive episode (SCID-defined) or euthymic, prospectively defined as ≤7 on both the 21-item Hamilton Depression Rating Scale ($HAMD_{21}$; Hamilton, 1960) and the Young Mania Rating Scale (Young *et al.* 1978) at initial assessment and after 1 month. Patients were excluded if they met criteria for any other current Axis I disorder (except anxiety) or substance dependence/abuse. All were receiving medication at the time of testing but this had remained stable for ≥4 weeks. For the MDD cohort, patients aged 18–65 years with a DSM-IV diagnosis of MDD, single episode or recurrent, were recruited from general practice clinics. For this latter (MDD) cohort, patients had been entirely psychotropic medication-free for at least 6 weeks before recruitment and were excluded if currently taking other medication active in the central nervous system, including beta-blockers or St John's wort, or if there was a co-morbid medical/psychiatric diagnosis, or recent alcohol/substance misuse. All were tested as soon as possible after recruitment to minimize delay in treatment. For all participants, illness characteristics, clinical ratings and medication history were determined by trained psychiatrists using full history, case-note and medication review and standardized rating scales. All studies were approved by the local National Health Service (NHS) Research Ethics Committee and all participants gave written, informed consent.

Neurocognitive testing

All participants completed the Vigil CPT (Cegalis & Bowlin, 1991) using the same parameters. In this task, a continuous stream of random letters of the English alphabet is displayed on a computer screen. Each letter appears for 85 ms, followed by a 900 ms inter-stimulus interval (ISI) and is presented as a white letter on a black background in the centre of the screen (see Fig. 1). Participants are instructed to look out for a target sequence (an 'A' immediately followed by a 'K') and must respond 'as quickly, but as accurately as possible' by pressing the spacebar if this target sequence occurs. The letter 'A' thereby becomes the signal for the potential occurrence of a target sequence, but responses should only be made once the second letter of the sequence, 'K', appears. In total, 480 letters are displayed, in which 100 target sequences occur. These are pseudo-randomized between each quarter of the test, i.e. so there are 25 targets within every 120 trials (The Psychological Corporation, 1998).

Data analysis procedure

Data extraction and cleaning

RT data were re-extracted from the original Vigil CPT output files and any responses were either classified as 'valid' or as 'commission error' according to their temporal relationship to the target sequence[1]†. Response

† The notes appear after the main text.

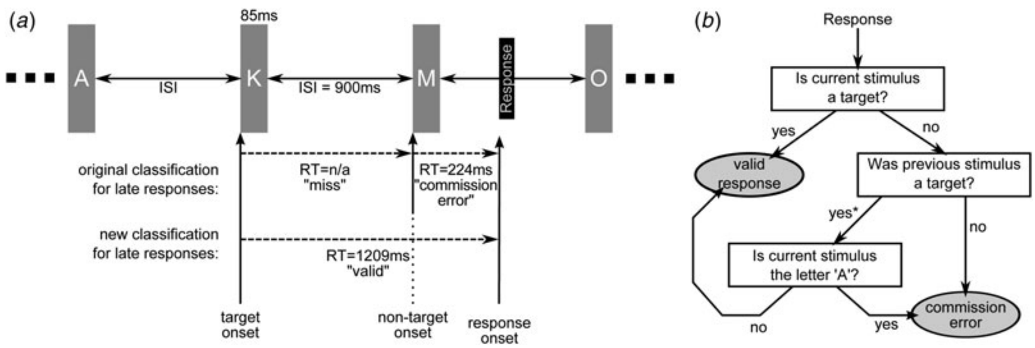

Fig. 1. The Vigil continuous performance test. Stimulus timing and example of a reclassification of a late response to a target sequence (*a*). General response classification rules (*b*). * If the previous stimulus was a target, the algorithm first checked if this target already had a valid response, in which case the current response was also classified as a commission error. This path is omitted in the figure. ISI, Inter-stimulus interval; RT, reaction time; n/a, not applicable.

times were always measured in relation to the onset of the second stimulus of a target sequence (letter 'K'). In contrast to the standard analysis, we classified responses as 'valid' even if they occurred after the onset of the letter that immediately followed a target sequence (see Fig. 1), allowing maximum response times of up to 1970 ms [i.e. (2 × ISI) + (2 × letter duration)]. However, there is one exception to this rule: since it is possible that two (or more) target sequences follow directly after another (i.e. 'A-K-A-K'), responses to the second 'A' would no longer be considered valid for the initial target sequence, as such a response could be a premature response to the new target sequence. Such responses were classified as commission errors. Any other responses that could not be associated with a target stimulus according to the above rules were also classified as commission errors. Target stimuli with no detectable valid response were classified as 'misses'.

This classification scheme ensured that responses with RT just above the ISI were considered (late) valid responses to the target, instead of resulting, according to the original scheme, in a 'miss'-classification to the target stimulus and a commission error for the stimulus following the target. While we believe that this classification better reflects the underlying psychological processes, it is important to consider the number of misses when looking at the distribution of response times of an individual. For instance, some individuals may have been better able than others to withhold responses when they detected that those responses would be late (i.e. after the onset of the stimulus following a target), thereby restricting their maximum response times to the 'standard' response window. Since such behaviour would reduce the potential range of RTs and therefore RT variability, care must be taken that this reduction does not come at a cost of an increased number of misses.

IIV analysis and ex-Gaussian modelling

From valid responses, basic measures of IIV were derived using the *iSD* – the SD of all RTs for each individual, and the *CoV* – the *iSD* divided by an individual's mean RT. Ex-Gaussian probability density functions were fitted to the distribution of valid response times of each individual using the DISTRIB toolbox (Lacouture & Cousineau, 2008) in MATLAB® v.R2010b (The MathWorks Inc., 2010). This toolbox uses maximum likelihood principles to estimate the ex-Gaussian distribution parameters *mu*, *sigma* and *tau*. Vincentile plots were also derived as a distribution-free representation of the data. For these data, RTs within each participant were ranked and eight Vincentiles derived (representing the average RT within each sequential 12.5% of valid data, from fastest to slowest). Individual Vincentiles were then averaged across participants.

Healthy control reference data

An SAS algorithm was used (Kosanke & Bergstralh, 1995) which sampled from the overall control cohort ($n = 138$) and matched controls to individual cases according to age, sex and National Adult Reading Test (NART)-estimated intelligence quotient (IQ) (Nelson, 1982). This created very closely matched healthy control groups for each of the three patient groups. Group analyses were made using SPSS v19 (USA).

Results

Subject demographics and clinical details

In total 297 datasets were available for analysis (see Table 1). This included 138 healthy controls (61 males, 77 females) and 159 patients. The three patient

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Table 1. *Demographic and clinical details*

	All healthy controls ($n = 138$)	BD euthymic ($n = 86$)	Control comparison ($n = 86$)[a]	BD depressed ($n = 33$)	Control comparison ($n = 33$)[a]	MDD ($n = 39$)	Control comparison ($n = 39$)[a]
Age, years	40.5 (12.54)	44.0 (9.74)	43.8 (9.61)	47.0 (8.64)	46.7 (8.42)	32.3 (10.11)	32.5 (10.37)
NART estimated IQ	111.1 (8.64)	110.9 (10.28)	111.4 (8.63)	109.0 (10.21)	109.8 (8.44)	108.2 (11.04)	109.1 (9.15)
$HAMD_{21}$	–	1.6 (1.66)	–	21.9 (5.75)	–	22.4 (5.29)	–
Age of onset, years	–	24.8 (7.12)	–	25.8 (13.23)	–	29.0 (8.65)	–
Diagnosis, n[b]							
Bipolar I	–	70	–	12	–	–	–
Bipolar II	–	16	–	16	–	–	–

Data are given as mean (standard deviation) unless otherwise indicated.

BD, Bipolar disorder; MDD, major depressive disorder; NART, National Adult Reading Test; IQ, intelligence quotient; $HAMD_{21}$, 21-item Hamilton Depression Rating Scale; SCID, Structured Clinical Interview for DSM-IV.

[a] Each control comparison was sampled from the overall control group (see Method), so are not independent.

[b] SCID-diagnosed bipolar type I or II (missing for $n = 5$ BD depressed).

samples included: 86 euthymic bipolar patients (41 males, 45 females), 33 depressed bipolar patients (19 males, 14 females) and 39 depressed MDD patients (15 males, 24 females). Data from one further female depressed MDD patient were excluded from the analysis as only 22% valid responses were recorded for this patient. The three patient groups and their respective matched control groups were closely matched for age and NART-estimated IQ ($p > 0.69$ for all).

None of the patients in the MDD group was currently on psychotropic medication; 24 (62%) had never previously taken antidepressant medication; of the remaining 15 (38%), the median time since last treatment was 12 months (range 2–84 months). Of the bipolar patients, five were drug-free at the time of testing. In the euthymic sample, 76 (88%) were taking a mood stabilizer (of which $n = 55$ lithium), 23 (27%) antidepressant medication, and 23 (27%) antipsychotic medication. In the depressed sample, 27 (84%) were taking a mood stabilizer (of which $n = 8$ lithium), 26 (81%) antidepressant medication, and 15 (47%) an antipsychotic medication. Medication details of one patient were not recorded.

Response profiles

Within the original raw dataset ($n = 296$), a total of 29 677 individual trials were recorded, of which 28 482 (96.0%) were responses within the originally defined response window (0–985 ms). The remaining 4.0% were classified as: early (300/29 677; 1.0%), i.e. responses that occurred before the 'K' of an 'AK' target sequence; or late (201/29 677; 0.7%), i.e. 'correct' responses which were slow (985–1970 ms)[2]; or misses (694/29 677; 2.3%). Examining these between patients and controls indicated that the greater proportion of early (226/300; 75.3%) and late responses (152/201; 75.6%), and misses (570/694; 82.1%) occurred in the patient sample. Comparing these directly revealed that, on average, significantly more misses occurred in all three patient samples compared with their respective control group, with depressed BD patients also making more early and late responses (see Table 2).

Following data cleaning (see above), averages of 94.4 (S.D. = 8.14) responses per participant in patients and 98.3 (S.D. = 3.11) responses per participant in controls were available for RT analysis.

Average RT

The analysis of the standard average RT showed significantly slower RT for the group of euthymic BD patients [$F_{1,170} = 6.322$, $p = 0.013$; $d = 0.38$, 95% confidence interval (CI) 0.08–0.68; see Table 2], but not for the group of depressed BD patients ($F_{1,64} = 1.009$, $p = 0.319$; $d = 0.25$, 95% CI −0.24 to 0.73) or the group of depressed MDD patients ($F_{1,76} = 0.048$, $p = 0.826$; $d = 0.05$, 95% CI −0.39 to 0.49) compared with controls.

IIV indices

The various measures of RT IIV are shown in Table 2. Analysis of the *iSD* demonstrated significantly greater variability in patients compared with their matched control data, for euthymic BD ($F_{1,170} = 4.785$, $p = 0.030$; $d = 0.33$, 95% CI 0.03–0.63), depressed BD ($F_{1,64} =$

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Table 2. *Descriptive statistics for RT data and response profile*

	All healthy controls ($n = 138$)	BD euthymic ($n = 86$)	Control comparison ($n = 86$)[a]	BD depressed ($n = 33$)	Control comparison ($n = 33$)[a]	MDD ($n = 39$)	Control comparison ($n = 39$)[a]
Average RT, ms	375.9 (69.08)	411.0 (75.56)*	382.7 (71.91)	412.9 (96.07)	390.9 (80.84)	382.7 (88.91)	378.3 (87.33)
iSD	83.6 (29.78)	95.9 (29.93)*	85.4 (33.34)	143.8 (56.21)***	80.7 (29.70)	104.8 (50.28)*	83.1 (26.53)
CoV	0.23 (0.08)	0.24 (0.07)	0.23 (0.09)	0.36 (0.14)***	0.21 (0.08)	0.27 (0.09)	0.23 (0.09)
Ex-Gaussian parameters							
Mu	310.0 (76.60)	332.2 (76.55)	316.0 (75.93)	296.0 (87.66)	324.6 (82.76)	298.5 (78.66)	309.4 (95.24)
Sigma[b]	32.1 (20.82)	37.7 (21.19)	33.2 (21.78)	45.2 (33.85)*	29.8 (18.46)	40.8 (39.62)	31.2 (17.97)
Tau	66.0 (29.14)	78.8 (32.55)*	66.8 (28.98)	117.3 (59.40)***	66.3 (22.32)	84.5 (47.67)	68.9 (28.71)
Response profile[c]							
Early response	0.54 (1.09)	0.70 (1.22)	0.62 (1.29)	3.06 (5.49)**	0.36 (0.99)	1.67 (4.16)	0.62 (1.60)
Late response	0.36 (0.93)	0.45 (0.84)	0.44 (1.12)	2.55 (2.66)***	0.30 (0.68)	0.74 (1.41)	0.26 (0.50)
Misses	0.90 (2.19)	3.77 (7.05)**	1.01 (2.65)	2.79 (3.66)*	0.88 (1.22)	3.95 (6.98)*	0.67 (0.98)

Data are given as mean (standard deviation).

RT, Reaction time; BD, bipolar disorder; MDD, major depressive disorder; *iSD*, individual standard deviation; *CoV*, coefficient of variation.

[a] Each respective control comparison was resampled from the overall control group ($n = 138$), so are not independent (see Method).

[b] For $n = 4$ datasets (1.3%), *sigma* was returned as 0 in the ex-Gaussian model.

[c] Mann–Whitney *U* test.

* $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.0001$ compared with respective control comparison data.

32.474, $p < 0.00001$; $d = 1.40$, 95% CI 0.85–1.92) and depressed MDD ($F_{1,76} = 5.662$, $p = 0.020$; $d = 0.54$, 95% CI 0.08–0.99). Accounting for the overall mean RT, a significantly greater *CoV* was observed in depressed BD ($F_{1,64} = 28.824$, $p < 0.00001$; $d = 1.32$, 95% CI 0.77–1.84). There was also a statistical trend for greater *CoV* for depressed MDD ($F_{1,76} = 3.545$, $p = 0.064$; $d = 0.43$, 95% CI −0.02 to 0.87), but no difference in euthymic BD ($F_{1,170} = 0.732$, $p = 0.393$; $d = 0.13$, 95% CI −0.17 to 0.43).

Ex-Gaussian analysis and Vincentile plots

The ex-Gaussian analysis indicated that there were differences across the three distribution parameters (see Table 2). No significant differences between patients and controls were observed in *mu* (euthymic BD: $F_{1,170} = 1.943$, $p = 0.165$; $d = 0.21$, 95% CI −0.09 to 0.51; depressed BD: $F_{1,64} = 1.864$, $p = 0.177$; $d = -0.34$, 95% CI −0.82 to 0.15; depressed MDD: $F_{1,76} = 0.301$, $p = 0.585$; $d = -0.12$, 95% CI −0.57 to 0.32). No significant differences in the *sigma* parameter were observed for euthymic BD ($F_{1,170} = 1.918$, $p = 0.168$; $d = 0.21$, 95% CI −0.09 to 0.51) or depressed MDD ($F_{1,76} = 1.901$, $p = 0.172$; $d = 0.31$, 95% CI −0.14 to 0.76), but *sigma* was significantly increased in depressed BD ($F_{1,64} = 5.292$, $p = 0.025$; $d = 0.57$, 95% CI 0.07–1.05). A significant increase in the exponential part of the RT distribution was observed for both BD patient groups: the *tau* parameter was greater in euthymic BD patients ($F_{1,170} = 6.604$, $p = 0.011$; $d = 0.39$, 95% CI 0.09–0.69) and depressed BD patients ($F_{1,64} = 21.347$, $p < 0.0001$; $d = 1.14$, 95% CI 0.60–1.64) compared with controls. There was also a statistical trend for greater *tau* in depressed MDD patients ($F_{1,76} = 3.034$, $p = 0.086$; $d = 0.39$, 95% CI −0.06 to 0.84).

Vincentile plots are shown in Fig. 2, providing convergent support for the ex-Gaussian analyses. For the euthymic BD sample, the plots for patients and controls remain close until the last Vincentile (V_8) where they diverge more sharply. This occurs more clearly in the depressed MDD and BD samples, particularly the latter. However, there are also differences evident in the first Vincentile (V_1) for the depressed samples, with responses being faster in patients than controls (a difference which is significant in the BD depressed sample; $p = 0.024$).

To facilitate comparison between patient groups, the ex-Gaussian parameters for euthymic BD, depressed BD and MDD groups were expressed as a *z*-score based on the mean and S.D. of their respective control groups. One-way analysis of variance revealed significant differences for *mu* ($F_{2,155} = 4.348$, $p = 0.015$) and *tau* ($F_{2,155} = 15.545$, $p < 0.0001$). *Post hoc* contrasts revealed that the *mu* parameter was significantly different between euthymic and depressed BD groups ($p = 0.006$) with a trend between euthymic BD and MDD groups ($p = 0.085$). For *tau*, the depressed BD group differed

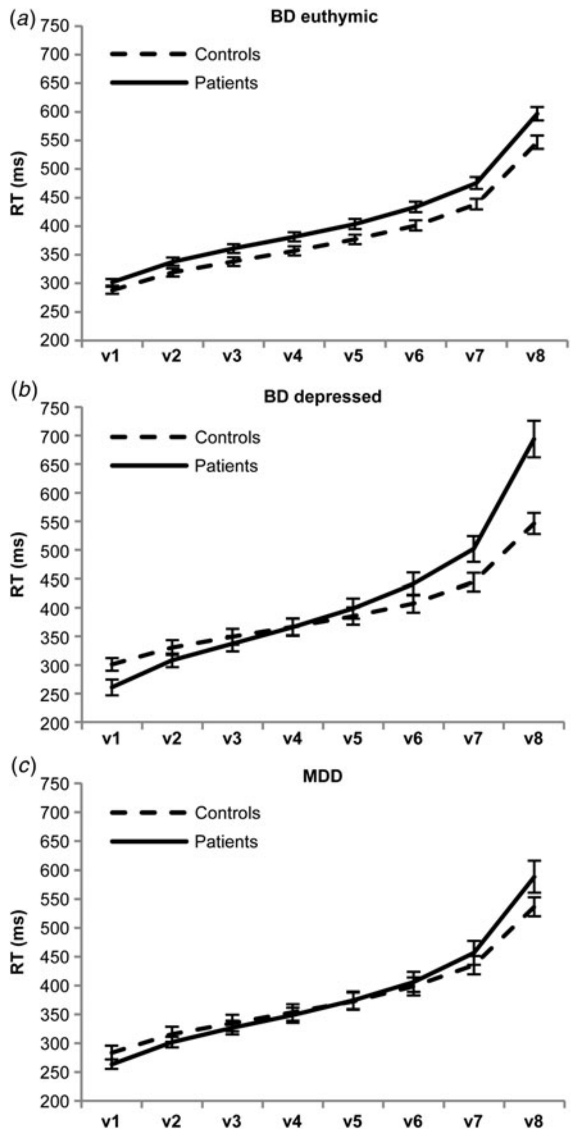

Fig. 2. Vincentile plots for all clinical groups compared with matched control data: (*a*) bipolar disorder (BD) euthymic; (*b*) BD depressed; (*c*) major depressive disorder (MDD). V1–V8 denote each Vincentile [sequential 12.5% of reaction time (RT) data] from fastest to slowest RT. Values are means, with standard errors represented by vertical bars.

significantly from both euthymic and MDD groups ($p < 0.001$).

Receiver operating characteristic (ROC) analysis

To demonstrate the degree of differentiation between the clinical groups and controls (i.e. that differences are not consequent to extreme responses from a small number of participants), an ROC plot (Wilcoxon estimate) was used to determine the optimum cut-point to maximize sensitivity and specificity. For MDD patients, a *tau* value of 56.12 yielded a ROC area under the curve (AUC) = 0.60 (95% CI 0.46–0.73), with sensitivity = 0.74 and specificity = 0.44. For euthymic BD patients, a *tau* value of 56.35 yielded a ROC AUC = 0.62 (95% CI 0.53–0.70), with sensitivity = 0.77 and specificity = 0.44. For depressed BD patients, a *tau* value of 85.56 yielded a ROC AUC = 0.82 (95% CI 0.70–0.93), with sensitivity = 0.73 and specificity = 0.88. Comparing between the clinical groups, the *tau* parameter also differentiated depressed from euthymic BD patients with sensitivity = 0.70 and specificity = 0.71 (ROC AUC = 0.73, 95% CI 0.61–0.84), and depressed BD from depressed MDD patients with sensitivity = 0.73 and specificity = 0.65 (ROC AUC = 0.68, 95% CI 0.55–0.82).

Relationship to severity of depression

Exploratory Spearman's correlations were performed separately for each patient group, between IIV parameters and the $HAMD_{21}$. No significant correlations between *iSD, CoV* or ex-Gaussian parameters were observed in euthymic ($-0.073 \leq r_s \leq 0.188$, $p > 0.080$ for all) or depressed BD patients ($-0.135 \leq r_s \leq -0.017$, $p > 0.450$ for all). For MDD patients, a near-significant positive correlation between depression severity and *CoV* was observed ($r = 0.314$, $p = 0.051$).

Discussion

The present study investigated RT IIV during a simple sustained attention task in three groups of patients with mood disorders: euthymic BD, depressed BD and depressed MDD. All three groups showed evidence of increased response variability compared with matched controls. Euthymic BD patients had greater values of *iSD* and *tau*, but not in *CoV* or *sigma*. Together with the fact that this group also showed greater standard average RT, but not in the fitted *mu* parameter, these results indicate that the differences between these patients and controls is best characterized as in increase in the exponential part of the RT distribution (i.e. an increased number of 'disproportionately slow' responses), as this would cause a shift in mean RT and *iSD* but not in *CoV*. Depressed BD patients showed the most consistent evidence of increase in RT variability, as all four indices of variability (*iSD, CoV, sigma* and *tau*) were significantly increased in comparison with the healthy control sample. It may at first seem surprising that there was no significant increase in average RT in this group as a result of increased variability. However, as can be seen in the Vincentile plot of this group, the increase in variability was due not only to an increase in the number of slow responses (similar to euthymia), but also the number of fast responses (although not to a sufficient extent to alter *mu*). Depressed MDD patients showed the weakest evidence for a RT variability increase.

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While the *iSD* was significantly higher in this group, both the *CoV* and the *tau* parameter showed only statistical trends for larger values. There were no differences in average RT, *mu* or *sigma*.

These data are in line with previous reports of increased IIV in attentional performance in BD (Bora *et al.* 2006; Brotman *et al.* 2009). However, to our knowledge this is the first study to comprehensively examine RT distribution parameters and IIV across patients with mood disorders. Previous studies have applied ex-Gaussian RT modelling to tasks in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). The *tau* parameter has been suggested to produce excellent differentiation between ADHD and controls (Leth-Steensen *et al.* 2000). Subsequent findings suggest that there are differences in all three parameters compared with controls, with more variability (*sigma*) and increases in *mu* and particularly slow (*tau*) responses – the latter suggested to reflect attentional lapses in some but not all trials (Hervey *et al.* 2006). In the present study, while there was no significant difference in *mu* between patients and controls, the Vincentile plots did indicate some evidence of faster responses in V_1 in the depressed samples (which was significant in BD depression). There was also a significant increase in the number of misses in all patient groups (and early and late responses, in depressed BD), compared with controls. This general inconsistency combined with the frequency of disproportionately slow responses is again consistent with 'phasic' attentional task engagement/disengagement. This has been suggested previously during CPT task performance in euthymic BD patients (Robinson *et al.* 2013). Functional imaging has further revealed that while prefrontal activation occurs early during CPT performance in mania, it cannot be maintained over sustained periods (Fleck *et al.* 2012).

An area of ongoing debate is the extent to which RT distribution characteristics can be linked to specific aspects of neurocognitive function. For example, the utility of ex-Gaussian modelling has been demonstrated across different conditions of the classic Stroop test, revealing attentional shifts which would otherwise be missed with outcomes based on simple central tendency (Heathcote *et al.* 1991). These authors suggest that no direct attribution can be made between 'parameter and process' and while 'the ex-Gaussian model describes RT data successfully, it does so without the benefit of an underlying theory' (Heathcote *et al.* 1991). However, more recently it has been proposed that the *tau* parameter is strongly related to 'higher' cognitive functions (a statistical composite measure of working memory tasks and reasoning) and is therefore a marker of individual differences in attentional/executive control (Schmiedek *et al.* 2007). As work in this area progresses – and if IIV and ex-Gaussian measures are applied more frequently in clinical studies – it may be possible to derive more precise theoretical accounts, informing our understanding of neurocognition in mood disorders.

A strength of the present study was the assessment of IIV and application of RT modelling to one single attentional CPT which had been used consistently in a series of studies in the same research centre. However, it should be noted that in addition to attention, other cognitive processes such as processing speed have been assessed as putative cognitive endophenotypes in BD (Antila *et al.* 2011; Daban *et al.* 2012). One caveat is that most studies have used the digit–symbol task as an index of processing speed, but this measure is known to involve multiple interacting lower-level and higher-level cognitive control processes, including executive control and attention (Cepeda *et al.* 2013). Therefore when utilizing such tasks in the search for candidate endophenotypes, especially if proposing process-specificity, it is necessary to consider more precisely the cognitive processes underpinning performance on any given measure. It is also important to ascertain whether IIV and shifts in the RT distribution in mood disorders are sensitive to the demand characteristics of tasks, such as rate of presentation or cognitive load, and therefore whether they are related more to impairments in attentional control or basic processing efficiency.

Other methodological considerations should be highlighted. The present study utilized a large normative reference sample from which control data were selected by computer algorithm and demographically matched to individual patient cases. This ensured very close group-wise matching of patients and controls which was independent of experimenter selection. The majority of BD patients in the present study were taking psychotropic medication at the time of testing. While several studies have reported minimal effects of medication on performance (Goswami *et al.* 2009; Bourne *et al.* 2013), the potential impact of medication on performance should be considered and replication in medication-free samples or in cohorts large enough to perform subgroup analysis is needed. The depressed MDD sample in the present study was entirely psychotropic medication-free at the time of testing and some evidence of increased IIV was observed, specifically *iSD*, but the ex-Gaussian parameters were not significantly different from controls (although *tau* was increased at a trend level, with a small to medium effect size). Differences in clinical characteristics (see Porter *et al.* 2003), such as medication, age (the MDD patients were younger) and number of episodes (the majority of MDD patients being first-episode) mean that comparisons need to be interpreted cautiously. Similarly the inherent difficulty in how to equate stage of illness and other clinical characteristics between MDD and BD in order to reliably compare them should also be noted, along with the issue of statistical power in relation to the sample size characteristics.

The clearest comparison between IIV parameters can be made between the BD groups. It is of note that variability is evident in euthymia (as increased *iSD* and *tau*) but increases in depression, reflected in the additional increase in *CoV* and *sigma*. It would be of interest for future studies to explore the potential neurobiological mechanisms underlying such effects. For example, it has been demonstrated in animal and human models that corticosteroid (cortisol) levels can exert both positive and negative effects on attention, depending on the relative occupancy of corticosteroid receptors (Lupien & McEwen, 1997). Given the evidence of hypothalamic–pituitary–adrenal (HPA) axis dysfunction and hypercortisolaemia in BD (Rybakowski & Twardowska, 1999; Gallagher *et al.* 2007), which is present in euthymia but worse in depression, examining the hypothesized role of systems such as the HPA axis and their potential for causing or exacerbating state-related effects is warranted.

Due to the methodological issues outlined it remains to be established if specific features of cognitive processes, such IIV in sustained attention, could be considered as cognitive endophenotypes. It has previously been suggested that impairment on tasks such as the CPT is more an indicator of general brain dysfunction, underpinning the attentional system, than a disorder-specific marker (Rosvold *et al.* 1956; Riccio *et al.* 2002). Given the strong relationship that has been identified between IIV and white matter, it is possible that some measures of IIV or components of the RT distribution such as *tau*, are sensitive markers of general white matter integrity (Fjell *et al.* 2011; Jackson *et al.* 2012; Tamnes *et al.* 2012). These links warrant detailed exploration in future studies – especially in combination with focused processing speed and attentional assessment – to ascertain the utility of these measures as markers of structural and functional integrity in a variety of clinical disorders in which white matter impairments are implicated, such as neurodegenerative and mood disorders (Sachdev *et al.* 2005; Assareh *et al.* 2011; Poletti *et al.* 2015). Including assessment in individuals with genetic risk, for example for mood disorder, will further inform the extent to which they can be considered endophenotypic markers (Hasler *et al.* 2006). Developing understanding of the relationship between specific cognitive processes and their structural and functional underpinnings has clear clinical implications, especially in the potential use of neurocognitive function in the stratification of mood disorders (Insel *et al.* 2010).

The present study has demonstrated increased RT IIV in sustained attention in mood disorders. Further analysis of RT distribution parameters revealed differences in the parameters affected between MDD and BD, and depression and euthymia in BD. These data highlight the utility of applying measures of IIV to characterize cognitive variability and the potential for future application in studies examining neurocognitive dysfunction and its underlying functional and structural brain connectivity in mood disorder.

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Declaration of Interest

None.

Notes

[1] This was done to permit the analysis of RT in relation to the intended target, independent of ISI. In typical analysis of continuous attention tasks, the RT is limited to a maximum ≤ ISI ms. For example, if a participant is slow to recognize given target sequences and make a response, even though their responses may be initiated validly by targets, they will be incorrectly recorded as errors if a subsequent letter is presented before their response can be completed. Most often these will appear as very fast commission errors.

[2] As this method of classification recoded the majority of what would previously have been considered 'commission errors' into 'correct-late' responses, in the present analysis commission errors were very infrequent and not considered further.

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