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Impaired sustained attention and executive dysfunction: bipolar disorder versus depression-specific markers of affective disorders

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Bipolar disorder is one of the most debilitating of all illnesses (Murray & Lopez, 1996). It is associated with poor prognosis and high mortality rate (Baldessarini & Tondo, 2003). One reason for the poor prognosis is the frequent misdiagnosis of the disorder (Bowden, 2001) especially in patients presenting with depression and no clear history of mania which results in inadequate treatment (Bowden, 2001; Ghaemi, Ko, & Goodwin, 2002; Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). Increased accuracy in diagnosing bipolar disorder can be best achieved by the identification of objective biological markers, reflecting underlying neural mechanisms that underlie core clinical features of the disorder, that are both persistent (i.e present across different mood states) and specific to bipolar disorder (i.e not present in unipolar depression). Neurocognitive task performance measures are valuable and easily obtainable indirect measures of function within neural systems supporting different domains of cognition. Examination of abnormalities in performance on specific neurocognitive tasks in individuals with bipolar disorder and those with unipolar depression can therefore provide valuable insights into neural mechanisms that differ between these two illnesses and that can ultimately provide objective biological markers needed to help improve diagnostic accuracy for bipolar disorder and unipolar depression. We next review the literature that has provided some evidence for persistent patterns of neurocognitive task performance abnormalities in bipolar disorder, and for distinguishable patterns of abnormalities on these measures in bipolar and unipolar depression, in domains of cognition that are relevant to understanding neural mechanisms underlying core symptoms of these illnesses.

Examples of domains of cognition relevant to understanding neural mechanisms of bipolar disorder and unipolar depression include memory, attention, and executive function, a term used interchangeably with cognitive control, that refers to higher-level cognitive functions involved in the control and direction of memory and attention in order to flexibly organize behavior and engage in forward planning (Stuss and Levine 2002, Clark et. al 2009). These domains are all key component subprocesses of emotion regulation, a core abnormality in both bipolar disorder and unipolar depression (Phillips, Ladouceur, & Drevets, 2008). There is strong evidence, for example, that bipolar disorder is associated with neurocognitive deficits including impaired executive function, sustained attention and short-term memory during acute phases of the illness and remission (Bearden, Hoffman, & Cannon, 2001). Several studies also examined the extent to which impairments in executive function, sustained attention and short term memory may represent objective markers of bipolar disorder that persist across different mood states (Clark, Iversen, & Goodwin, 2002; Clark, Kempton, Scarna, Grasby, & Goodwin, 2005; Ferrier, Stanton, Kelly, & Scott, 1999; Liu, et al., 2002; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2007; Rubinsztein, Michael, Paykel, & Sahakian, 2000). Other studies examined the extent to which impairments in these different neurocognitive domains were also present in unipolar depression (Borkowska & Rybakowski, 2001; van der Meere, Borger, & van Os, 2007; Wolfe, Granholm, Butters, Saunders, & Janowsky, 1987). The above studies specifically reported impaired executive function in bipolar depression, which exists to a greater extent than in unipolar depression (Borkowska & Rybakowski, 2001), although at least one study indicated no difference between unipolar and bipolar depression on executive function (Gruber, Rathgeber, Braunig, & Gauggel, 2007). A number of studies and a recent meta-analyses reported that impaired executive function persists in remission in bipolar disorder (Ferrier, et al., 1999; Mur, et al., 2007; Rubinsztein, et al., 2000), and is present in first degree relatives of patients with bipolar disorder (Clark, Sarna, & Goodwin, 2005). The persistence of impaired executive function during remission in bipolar disorder was not confirmed in all studies, however (Clark, et al., 2002). Findings indicate impaired executive function in unipolar depression (Elliott, et al., 1996; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999) that is independent of medication status (Taylor Tavares, et al., 2007). The degree of executive impairment may be specific to symptom dimensions such as apathy (Feil, Razani, Boone, & Lesser, 2003), and may be independent of symptom severity (Porter, Gallagher, Thompson, & Young, 2003). Impaired executive function improves significantly with remission in patients with unipolar depression, although residual deficits may remain to some degree (Clark, Sarna, et al., 2005).

Studies have also reported impaired sustained attention in bipolar disorder during mania, remission and in first degree relatives of patients with bipolar disorder (Clark, et al., 2002; Clark, Kempton, et al., 2005; Liu, et al., 2002). Impairment during remission, appears to be medication-independent and manifests as decreased target sensitivity on a sustained attention task whereas impairment during mania manifests as increased false responding and perseveration and is partly explained by the impact of medications (Bora et. al 2006). The few studies that examined sustained attention in bipolar depression indicate impairments in this domain in medicated bipolar depressed patients (Holmes, et al., 2008). Findings in unipolar depression, by contrast, indicate possible impairment in this domain (van der Meere, et al., 2007), which may subside in partially and completely remitted patients (Clark, Kempton, et al., 2005; Liu, et al., 2002).

There is evidence that short-term memory is disrupted in bipolar depression (Sweeney, Kmiec, & Kupfer, 2000), potentially more than in unipolar depression (Wolfe, et al., 1987). This may be state-specific (Ferrier, et al., 1999), although some studies detected persisting short-term memory impairments in remission (Rubinsztein, et al., 2000). Short-term memory dysfunction increases with illness duration and number of mood episodes (Bearden,

et al., 2006), and may predict functional outcome (Martinez-Aran, et al., 2004). Consolidation of short-term memory into long term storage is impaired in unipolar depression (Wolfe, et al., 1987). This impairment may subside during remission (Clark, Sarna, et al., 2005), increase with illness chronicity and correlate with the total length of time spent in a depressed state in unipolar depression (Gorwood, Corruble, Falissard, & Goodwin, 2008). This deficit may be related to the progressive hippocampal degeneration in unipolar depression (MacQueen, et al., 2003).

A major problem with these previous studies is that they were not specifically designed to directly compare different groups of bipolar and unipolar depressed individuals, in order to examine the extent to which impairments in these neurocognitive domains represented specific and persistent objective markers of bipolar disorder, and therefore did not include both bipolar disorder patients in different mood states and depressed patients with unipolar depression (Clark & Sahakian, 2008). An additional problem with these studies is that they employed different tasks to measure function within these cognitive domains, which makes it extremely difficult to directly compare findings among them. We therefore wished to determine the extent to which dysfunction in these three different neurocognitive domains were evident in different mood states in bipolar disorder, and whether they were present in unipolar depression. We employed well-validated computerized tests of the three cognitive domains that were administered to four groups of participants: Bipolar euthymic (Beuth), bipolar depressed (Bdep), unipolar depressed (Udep) and healthy controls (HC).

Our specific aims were twofold:

1. To determine the extent to which abnormalities in these three cognitive domains were persistent markers of bipolar disorder. We hypothesized that Beuth would show impaired sustained attention relative to HC, while Bdep would show impaired executive function relative to HC. Existing data did not allow us to specify whether Bdep would show similar level of impairment on sustained attention as Beuth, or whether impaired executive function would characterize Bdep but not Beuth.
2. To determine the extent to which abnormalities in any of our three cognitive domains distinguished bipolar from unipolar depression. We hypothesized that both Bdep and Udep would show impaired executive function and short-term memory relative to HC. Existing data did not allow us to specify whether impaired sustained attention would characterize Bdep but not Udep.

Methods

Participants

The study protocol was approved by the University of Pittsburgh Institutional Review Board. 32 outpatients meeting criteria for bipolar disorder type I according to DSM-IV and diagnosed using the Structured Clinical Interview for DSM-IV, Research Version participated in the study. 18 participants were in remission and euthymic (Beuth) at the time of testing with a Young Mania Rating Scale (YMRS) score≤10 and a 25-item Hamilton Depression Rating Scale (HDRS-25) score≤7, 14 participants were in depressed episode (Bdep; HDRS-25≥17). All participants had experienced at least two episodes of depression or mania in the last 4 years. In addition, 20 patients with recurrent unipolar depression (Udep), currently in depressed episode (HDRS-25>17) and 28 healthy control participants (HC) with no previous psychiatric history or psychiatric history in first and second degree relatives were enrolled in the study. The groups were age, gender-ratio and IQ-matched (Table 1). A record of participants' medications from the day of testing or up to 30 days prior was used; this information was missing in 10 participants (4 Bdep, 3 Beuth and 3 MDD). Exclusion criteria included a history of head injury, neurological disorder

(cardiovascular accident, epilepsy, dementia, developmental disorder, loss of consciousness for more than ten minutes), cognitive impairment (score<24 on Mini-Mental State Examination) (Folstein, Folstein, & McHugh, 1975), premorbid IQ estimate<85 (National Adult Reading Test), (Nelson HE, 1991) current alcohol and illicit substance abuse (determined by saliva and urine screen) and Axis-II borderline personality disorder. Additional exclusion criteria for HC included history of alcohol and illicit substance dependence. The participant population reflected the demographics of Pittsburgh and were recruited through the Western Psychiatric Institute and Clinic, Mood Disorder Treatment and Research Program and local advertising. All participants were made aware of the purpose of the study and signed informed consent to participate. Clinical characteristics of each of the study groups are shown in table 1.

We also calculated a medication load index, a measure that has been previously used to assess for medication effect in neuroimaging studies (Versace et. al 2008). In calculating this index, antidepressants and mood stabilizers are categorized into low-dose and high-dose groupings and antipsychotics are converted to chlorpromazine hydrochloride dose equivalents and benzodiazepine dose is coded relatively to the recommended daily dose by the Physicians′ Desk Reference. A Composite measure of medication load is then calculated by summing up all individual medication codes. Medication data was missing for 3 Beuth, 3 Bdep and 3 Udep participants (table 1.)

Computerized tasks—We employed three computerized neurocognitive tasks from the Cambridge Neuropsychological Tests Automated Battery (CANTAB): (a) Rapid Visual Processing (RVP) task, as a measure of sustained attention; (b) Stockings of Cambridge (SOC) task, as a measure of executive function; and (c) Delayed matching to Sample task (DMS), as a measure of memory. These are valid tasks to use in healthy individuals and those with neuropsychiatric disorders (Sahakian & Owen, 1992).

Rapid Visual Processing Task (RVP): A white box is displayed in the center of the computer screen, inside which digits, from 2 to 9, are displayed randomly at the rate of 100 digits per minute. Participants must detect consecutive odd or even sequences of digits and respond by pressing the touch pad. Participants press the touch pad when they detect any of the following three sequences of three consective digits (2-4-6, 3-5-7, 4-6-8). The primary outcome measures are mean latency, total hits and total false alarms and the duration of the task is 7 minutes.

Stockings of Cambridge (SOC): Participants are shown two displays containing colored balls. The displays are described as stacks of colored balls held in socks suspended from a beam. Participants must use the balls in the lower display to copy the pattern shown in the upper one. The balls may be moved one at a time by touching the required ball then touching the position to which it should be moved. The primary outcome measures are mean number of moves for 3, 4 and 5-move problems.

Delayed matching to Sample (DMS): This is a test of immediate and delayed visual memory, in a four-choice simultaneous and delayed recognition memory paradigm. Participants are shown a complex visual pattern (the sample) and then four different patterns only one of which is identical to the sample. In some trials the sample and the choice patterns are shown simultaneously, whereas in others, there is a delay of 0, 4 or 12 seconds. Participants are instructed to touch the pattern that matched the sample. The primary outcome measure is percentage of total correct responses.

Statistical Analyses—Analyses were conducted using the Statistical Package for Social Sciences, Version 16. We first examined the overall effect of group on each outcome

measure for each task using four-way analyses of variance. If there were a significant group effect, we then performed specific pair-wise post-hoc analysis using Bonferroni's test to compare 1. Beuth, Bdep and HC, to test our first main hypothesis and 2. Bdep, Udep and HC to test our second main hypothesis. In exploratory analyses, Pearson correlation analyses were performed between abnormal measures on each task in Beuth, Bdep and Udep and HAM-D scores, YMRS scores, illness duration, age of illness onset and number of depressive and manic episodes. Potential confounding effect of medications in each patient group was examined using independent t-tests to compare relevant dependent measures in participants taking, versus those not taking, each class of medication (antipsychotics/mood stabilizers/antidepressants/anxiolytics) and by running correlation analyses between medication load index and relevant abnormal measures in each participants group. Potential confounding effect of comorbidites on task performance was examined by using independent t-tests to compare performance of subjects with and without a specific comorbidity within each group on the relevant tasks. For all comparisons, statistical significance was set at $p<0.05$.

Results

There were significant main effects of group upon the following outcome measures: RVP total hits (p=0.001) and SOC number of moves for 4 move-problems (NM4M) (p=0.016).The four groups were not different on RVP total false alarms, RVP mean latency, SOC number of moves for 3-move and 5-move problems (NM3M and NM5M) and DMS percentage of total correct responses (p >0.05) (Table 2.). We then performed relevant pair wise comparisons between groups to test our two main hypotheses:

Comparing Beuth, Bdep and HC to test Hypothesis 1

1-SOC: A measure of Executive function—Bdep, but not Beuth, were impaired relative to HC. Bdep had higher NM4M compared to HC (p= 0.046,Cohen's d=0.83) (Figure 1b.). Beuth did not differ from HC on this measure (p>0.05).

2- RVP: A measure of sustained attention—Bdep and, to a lesser extent, Beuth, had fewer hits than HC (p=0.001, Cohen's d=1.5 and p= 0.045, Cohen's d=0.8, respectively) (Figure 1a.). The four groups did not differ significantly on false alarms and mean latency, hence no post-hoc pair-wise comparison was conducted.

3-DMS: A measure of short-term memory—The four groups did not differ significantly, hence no post-hoc pair-wise comparison was conducted.

Comparing Bdep, Udep and HC to test Hypothesis 2

1- SOC: A measure of Executive function—Both Udep and Bdep were impaired relative to HC. Both Bdep, as above, and Udep had higher NM4M relative to HC (p=0.045, Cohen's d=0.88 for Udep vs HC) (Figure 1b).

2- RVP- a measure of sustained attention—Bdep differed from HC on total hits as above, but Udep did not differ significantly from HC on this measure (p>0.05) (Figure 1a.).

3-DMS: A measure of short-term memory—The four groups did not differ significantly, hence no post-hoc pair-wise comparison was conducted.

Exploratory Analyses examining relationships between abnormal task performance and clinical variables in patient groups: There were no significant relationships in both Bdep and Udep between illness duration, age of illness onset, depression severity or number

of depressive episodes and SOC NM4M (p>0.05). Bdep taking antipsychotics (AP) and anxiolytics (AX) had higher NM4M relative to Bdep not taking AP or AX (p= 0.005 and 0.023, respectively) There were no significant relationships between medication class and NM4M in Udep (p>0.05).

There were no significant relationships in both Beuth and Bdep between illness duration, age of illness onset, depression severity, number of depressive or number of manic episodes and RVP total hits (p>0.05 for all correlation analyses). RVP total hits did not differ between subjects on and off each class of medication in Beuth and Bdep (p>0.05 for all comparisons). There was a statistically significant negative correlation between RVP total hits and medication load index in Beuth (r=- 0.628, p= 0.012). No other significant correlations between medication load index and abnormal measures were shown in any group

In regards to confounding effect of comorbidites, we found no difference (p> 0.05) within Bdep on SOC NM4M and RVP total hits between subjects with and without lifetime history of substance abuse/dependence on one hand and those with and without comorbid anxiety disorders on the other hand. We also found no difference within Beuth on RVP total hits between those with and without comorbid substance use and those with and without comorbid anxiety disorders and there was also no difference within Udep on SOC NM4M between subjects with and without comorbid substance use and those with and without comorbid anxiety disorders.

Discussion

The overall goal of this study was to employ neurocognitive tasks to obtain indirect measures of function within neural systems supporting different domains of cognition in individuals with bipolar disorder and those with unipolar depression to provide valuable insights into neural mechanisms that may differ between these two illnesses. This can ultimately provide the objective biological markers needed to help improve diagnostic accuracy for bipolar disorder and unipolar depression. To achieve this goal, we examined in Beuth, Bdep, Udep and HC performance on well-validated neurocognitive tasks measuring three cognitive domains that are relevant to understanding neural mechanisms underlying emotion dysregulation, a key feature of these illness: executive function, sustained attention, and memory.

Our findings regarding executive function show that Udep and Bdep were impaired on the SOC task relative to HC. Impairment was evident on a moderately-difficult component of the task in which both Udep and Bdep had more NM4M than HC. In contrast, Beuth performance on this task did not differ from HC. The easiest and the most difficult task components, 3-move-problmes and 5-move-problems respectively, did not differentiate either depressed group from HC, suggesting potential ceiling and floor effects for performance on these task components. Indeed, 86 % of our participants solved the 3-move-problems with 3 or 4 moves, suggesting a ceiling effect for this part of the task. In addition, 25 % of participants used 6 or more moves (i.e 2 or more extra moves) to solve the 4-move-problems compared to 50% of subjects who used 7 or more moves (i.e 2 or more extra moves) to solve the 5-move-problems suggesting a floor effect for the latter. These findings therefore suggest that executive dysfunction may be a depression-specific, but not bipolar disorder-specific, impairment that is present in Udep and Bdep but not in Beuth. This is consistent with previous findings (Borkowska & Rybakowski, 2001; Clark, et al., 2002), although some studies reported executive dysfunction in remitted bipolar patients (Ferrier, et al., 1999; Mur, et al., 2007). The association of impaired executive function with depressed mood state regardless of diagnosis may reflect an impaired ability to perform externally-

focused cognitive control processes necessary for emotion regulation, that is therefore manifest in both bipolar and unipolar depression. The deleterious impact of depressed mood because of the load associated with depression-related, negative self-focused cognitions may further impact executive dysfunction in both illnesses. It is well established that executive function is supported by different prefrontal cortical regions, including the dorsolateral prefrontal cortex (Adolph et. al 1996), regions that are implicated in effortful, voluntary emotion regulation (Phillips, Ladouceur and Drevets, 2008). Our findings therefore indicate that dysfunction in these regions may underlie emotion dysregulation and the development of depressed mood in both bipolar disorder and unipolar depression, and are consistent with neuroimaging studies reporting abnormal activity in these regions during emotion regulation tasks in both bipolar depressed (Deckersbach et al., 2008) and unipolar depressed adults (Fales et al., 2008; Siegle et al., 2002).

Our findings regarding sustained attention show that both Bdep and Beuth were impaired (less accurate) on the RVP task, although this was much more evident in Bdep. In contrast, Udep showed no statistically significant impairment. Our findings are consistent with previous studies indicating impaired sustained attention in euthymic individuals with bipolar disorder (Clark, et al., 2002; Clark, Kempton, et al., 2005), and medicated individuals with bipolar depression (Holmes, et al., 2008). Our study, however, is the first to suggest that impaired sustained attention may be bipolar-specific, rather than also present in Udep. The sustained attention deficit in bipolar disorder may reflect an underlying predisposition to distractibility or poor attentional control that in turn may lead to inability to direct attention away from distracting stimuli/environmental events which may manifest as emotional lability (Phillips et. al 2008), a clinical feature of individuals with bipolar disorder even during remission, but less characteristic of unipolar depression. Different prefrontal cortical regions, including anterior cingulate gyrus and dorsal prefrontal cortical regions have been implicated in different attentional tasks(MacDonald et. al 2003 & Carter et. al 1999). Our findings therefore suggest that persistent functional impairments within these regions may be one neural mechanism contributing to impaired sustained attention and emotional lability in bipolar disorder, and are consistent with the small number of neuroimaging studies that have reported functional abnormalities in prefrontal cortical regions during sustained attention tasks in remitted bipolar adults (Strakowski et al. 2004).

Our findings regarding short-term memory show this was not impaired in any patient group. This is in support of recent findings in Bdep (Holmes, et al., 2008). Although a number of studies demonstrated impaired short-term memory in bipolar disorder, the deficits appear to correlate with illness severity and duration spent in depressed state (Gorwood, et al., 2008; MacQueen, et al., 2003). It is therefore possible that participants in our sample were either too young, or did not have a long enough illness duration (mean 14.1-18.2 years) for short-term memory deficits to be apparent. A recent meta-analysis indicates that when short term memory deficit is found in bipolar participants, the effect sizes are small (Bora et. al 2009). There may, therefore, be a need to examine a much larger sample of individuals with bipolar disorder or unipolar depression to be able to detect these subtle changes.

It is to be noted that while Udep and Bdep differed significantly from HC on the executive function task, they did not differ significantly from Beuth, and while Bdep and Beuth differed significantly from HC on the sustained attention task, they did not differ significantly from Udep. A larger sample size may therefore be needed in future studies to demonstrate a difference between Udep vs (Bdep or Beuth) on RVP, and Beuth vs (Udep or Bdep) on SOC in order to confirm the specificity of these measures. We therefore calculated the sample sizes needed to demonstrate a difference between Udep vs (Bdep or Beuth) on RVP, and Beuth vs (Udep or Bdep) on SOC. The sample size needed to demonstrate a significant difference of moderate effect size between the relevant patients groups (d=0.5)

would be 51 per group assuming a power of 80%. While future studies can therefore aim to replicate our findings with larger sample sizes, we were able to detect large effect sizes (Cohen's d ≥ 0.8) with our current sample. Furthermore, when considering our *null* findings: Udep Vs HC on the sustained attention measure and Beuth vs HC on the executive function task, the statistical power for these statistical comparisons was 86% and 85%, respectively, given a statistical threshold of $p<0.05$, and an effect size comparable to the effect sizes we observed in our significant main between-group comparisons (Cohen's d ≥0.8). These findings indicate that we had adequate power for these analyses, reducing the likelihood of type II error.

A further limitation that is worth mentioning is our choice of neurocognitive tasks which was limited in an effort not to overburden our participants: As discussed in the Introduction, executive function is a complicated construct that refers to higher cognitive processes involved in the control and direction of memory and attention in order to flexibly organize behavior and engage in forward planning. The visual planning task (Stocking of Cambridge) that we employed in our study measures one aspect of this multifaceted construct. In addition, in our choice of memory assessment, we limited our assessment to spatial short term memory, which represents one domain of memory. Another limitation of our study is the absence of information regarding attention deficit hyperactivity disorder (ADHD) in our sample which, if present, may have contributed to some of the cognitive deficits detected. Future studies are needed to explore the association between comorbid ADHD and cognitive deficits in bipolar disorder. One limitation, that is also common to other mid-life studies, is the fact that some Udep in our study may not have yet been past the age for possible development of bipolar disorder. Hence, future studies using similar tasks need to be conducted in older patients. In addition, it is possible that equating current IQ across all groups may have masked some cognitive deficits in bipolar and unipolar depressed groups in the study. We chose to equate IQ across groups in order to avoid the potential confounding effect of IQ differences across groups upon our measures of cognitive control in the present study. Future studies could, however, examine cognitive functioning in bipolar and unipolar depressed groups showing a wider range of current IQ. Previous studies reported an association between impulsivity and suicide attempts (Swann et. al 2005). Unfortunately we did not have an accurate measure of the number and nature of previous suicide attempts in all bipolar and unipolar depressed study participants and therefore could not measure relationships between suicide attempt history and our behavioral measures of impulsivity. This should be an aim of future studies.

A major limitation of prior studies examining neurocognitive deficits in bipolar disorder is the potential confound of medication effects. Limiting studies to unmedicated patients is not always possible because of the necessity of treatment with medications for many patients with bipolar disorder, especially those in depressed episode, and for patients with recurrent unipolar depression (Phillips, Travis, Fagiolini, & Kupfer, 2008). Indeed, patients included in our study were taking psychotropic medications due to severity of their illness, having experienced at least 2 affective episodes in the last four years. Our findings suggest, however, that only a small number of abnormal neurocognitive measures were associated with medications (mainly AP and AX) in Bdep and Beuth This is consistent with findings showing that psychotropic medications can be associated with worse cognitive performance (Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005). In a future study, we would also wish to include euthymic individuals with a history of recurrent unipolar depression, in order to compare performance on all the tasks in the present study in this group, Beuth, Bdep and Udep.

This is the first study to examine the extent to which impairment on three neurocognitive domains may represent persistent and bipolar disorder-specific markers of affective

disorders, by measuring performance on well-validated tasks of sustained attention, executive function and memory in Beuth, Bdep and Udep relative to HC. We show that impaired sustained attention appears to be bipolar disorder-specific and persistent across euthymic and depressed mood states, while executive dysfunction, by contrast, is present in Udep and Bdep but not Beuth, and therefore may be more likely to represent a marker of depression. The neurocognitive measures we employed in our study are easily-administered and transportable tasks that can be used in a variety of different clinical settings as indirect measures of function within neural systems underlying cognitive domains relevant to understanding pathophysiological processes that may distinguish bipolar disorder and unipolar depression.

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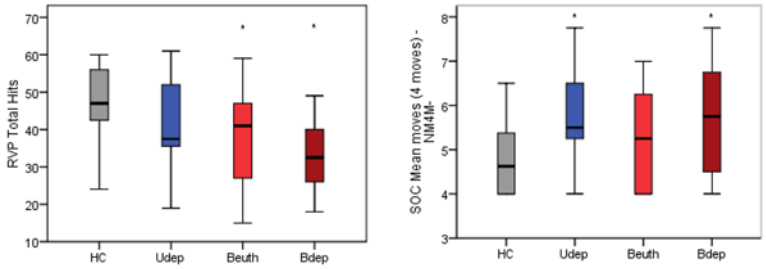

Fig 1. 1a- RVP Total Hits and 1b- SOC NM4M across groups

1a. RVP total Hits: HC (mean = 47.0, s.d= 9.3), Udep (mean= 41.1, s.d= 11.7), Beuth (mean= 38.1, s.d= 12.6), Bdep (mean= 32.8, s.d=9.8).

4-group ANOVA: F(3,76)=6.04, **p= 0.001**. Post hoc Bonferroni tests: **Bdep<HC, p=0.001, Beuth<HC, p=0.045**, for all other post-hoc comparisons p>0.1.

1b. SOC NM4M: HC (mean = 4.8, s.d= 0.8), Udep (mean = 5.6, s.d.= 1.0), Beuth (5.3, s.d= 1.0), Bdep (mean= 5.7, s.d.= 1.3).

4-group ANOVA: F(3,76)= 3.56, **p= 0.016**. Post hoc Bonferroni tests: **Udep > HC, p=0.045, Bdep > HC, p=0.046**, all other post-hoc comparisons p>0.1.

*p< 0.05 for post-hoc comparisons vs HC.

Table 1

Demographic and clinical data

	HC N=28	Beuth N=18	Bdep N=14	Udep N=20	Statistics*
Age	31.9 (9.4)	35.7 (8.9)	39.7 (10.2)	34.2 (9.4)	F (3,76)= 2.25 p=0.089
Female: Male	19:9	11:7	11:3	16:4	Chi-Square=2.17 df=3 p=0.537
IQ	115 (7)	113 (7)	112 (5)	110 (11)	F (3,76) =2.25 p= 0.089
HAM-D	-----	4.2 (4.1)	23.7 (8.0)	24.8 (5.8)	Udep vs Bdep: t=-048, df=31 p=0.634
YMRS	-----	2.1 (2.7)	3.0 (1.8)	4.2 (2.5)	F (2,37)=2.62 p=0.086
Duration of Illness	-----	18.2 (9.2)	16.3 (9.8)	14.1 (10.2)	F (2,49)=1.91 p=0.159
Number of Depressive Episodes§	-----	5.5 (4.1)	4.3 (4.4)	3.6 (2.4)	----------
Number of Manic Episodes§	-----	5.0 (3.7)	4.8 (3.4)	-----	----------
Age of Onset	-----	18.2 (6.9)	23.4 (9.6)	19.5 (6.7)	F (2,49)=0.82 P=0.447
Medication Load Index	-----	3.7 (2.0)	3.7 (2.8)	2.4 (1.7)	F(2,40)= 2.02 P=0.146
Subjects with Substance use disorders§§	-----	12	8	4	
Subjects with anxiety disorders§§	-----	7	3	7	

*4-way ANOVA for age and IQ, 3-way ANOVA for YMRS, duration of illness and age of onset, t-test for HAM-D, and Chi-Square for gender ratio

§Data regarding number of episodes is missing on 13 subjects (8 Bdep, 3 Beuth and 2 UDep)

§§Data regarding comorbidities is missing on total of 5 subjects (3 Bdep, 2 beuth) for substance abuse/dependence and 13 subjects (6 Bdep, 3 Beuth, and 4 Udep) for anxiety disorders.

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Table 2

Neurocognitive measures : 4-group comparisons

	HC n=28	Beuth n=18	Bdep n=14	Udep n=20	ANCOVA	Significant Post-hoc Bonferroni's tests and effect size (Cohen's d)
RVP Total Hits Mean (SD	47.0 (9.3)	38.1(12.6)	32.8 (9.8)	41.1(11.7)	**F(3,76)=6.04 p=0.001**	**Bdep<HC, p=0.001, d=1.5 Beuth<HC, p=0.045, d=0.8** Udep vs HC, p> 0.1, d= 0.5
RVP False alarms Mean (SD)	2.3 (2.6)	4.7 (4.3)	4.8 (7.5)	5.4 (8.4)	F=(3,74)=1.34 p=0.268	
RVP Latency Mean (SD)	401 (79)	445 (127)	470 (96)	437(72)	F(3,73)=1.87 p=0.142	
SOC # problems solved with Min moves (NPM) Mean (SD)	8.9 (1.8)	8.6 (2.0)	7.1 (2.9)	8.0 (1.9)	F(3,76)=3.68 P=0.053	
SOC # moves 3-moves(NM3M) Mean (SD)	3.4 (0.8)	3.1 (0.3)	3.9 (1.2)	3.5 (1.0)	F(3,75)=2.29 P=0.086	
SOC # moves 4-moves(NM4M) Mean (SD)	4.8 (0.8)	5.3 (1.0)	5.7 (1.3)	5.6 (1.0)	**F(3,76)=3.56 p=0.016**	**Udep > HC, p=0.045, d= 0.88 Bdep > HC, p=0.046,d= 0.83** Beuth vs HC, p>0.01, d= 0.55
SOC # moves 5-moves(NM5M) Mean (SD)	6.8 (1.4)	7.0 (1.3)	7.1 (2.1)	7.4 (1.7)	F(3,74)=0.415, p=0.743	
DMS % correct Mean (SD)	93 (7)	88 (11)	92 (10)	90 (10)	F(3,76)=1.13, p=0.343	