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Authors

Bomyea, Jessica A
Parrish, Emma M
Paolillo, Emily W
[et al.](#)

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Relationships Between Daily Mood States and Real-Time Cognitive Performance in Individuals with Bipolar Disorder and Healthy Comparators: A Remote Ambulatory Assessment Study

Jessica A. Bomyea, Ph.D.^{1,2}, Emma M. Parrish, B.S.^{2,3}, Emily W. Paolillo, M.A.^{2,3}, Tess F. Filip, B.A.², Lisa T. Eyler, Ph.D.^{1,2}, Colin A. Depp, Ph.D.^{1,2}, Raeanne C. Moore, Ph.D.²

¹ VA San Diego Healthcare System, San Diego, CA.

² Department of Psychiatry, University of California San Diego, San Diego, CA.

³ SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA.

Abstract

Objective: Neuropsychological impairments are observed in individuals with Bipolar Disorder (BD), yet knowledge of how cognitive deficits unfold in real-time remains limited. Given intraindividual variability in mood observed in people with BD, and the potential for mood and cognition to be mutually influential, we employed ambulatory assessment technologies to examine potential contemporaneous (same survey) and lagged (next survey) relationships of cognition and mood.

Methods: Outpatients with BD (n=46) or no psychiatric disorders (healthy volunteers [HV]; n=20) completed in-laboratory neurobehavioral assessments and 14 days of smartphone-administered mobile cognitive tests and ratings of affective variables. Linear mixed effects models were used to analyze real-time relationships between mobile cognitive test performance and mood.

Results: On in-laboratory tests, participants with BD showed worse cognitive performance than HVs as well as mild depression severity; mood and cognitive performance were unrelated. On mobile cognitive tests and surveys, participants with BD showed somewhat worse cognitive performance and ratings of lower energy and greater sadness relative to HV participants. Among those with BD, mania and sadness earlier in the day related to worse processing speed and better working memory performance, respectively, on the next survey. In contrast, same survey ratings of greater stress related to better working memory, and greater happiness related to better processing speed.

Address Correspondence to: Raeanne C. Moore, Ph.D., Department of Psychiatry, University of California, San Diego, 220 Dickinson Drive, St B (8231), San Diego, CA 92103-8231. r6moore@health.ucsd.edu. Phone: 619-543-5378. Fax: 619-543-1235.

Conflicts of interest

Dr. Raeanne C. Moore is a co-founder of KeyWise AI, Inc. and a consultant for NeuroUX. JB, EMP, EWP, TF, LE, and CD report no financial relationships with commercial interests.

Ethical Standards statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the ethics committee of each participating institution. The authors assert that ethical approval for publication of this report has been provided by their local Ethics Committee.

Conclusions: Real-time assessments of mood and cognition provide incremental information beyond what can be gleaned from laboratory assessments. Understanding how these affect-related changes in processing speed emerge and play out in daily life may provide clinically useful information for treatment planning.

Keywords

Neuropsychiatric Populations; Digital Neuropsychology; Depression; Mania; Mobile Health; Ecological Momentary Assessment

Introduction

Bipolar disorder (BD) is characterized by periods of mania, euthymia, and depression corresponding to affective and behavioral manifestations (e.g., poor impulse control; APA, 2013). Depression and mania each have potential to impede thinking, planning, and appropriately attending to the environment. Neuropsychological studies of individuals with BD document deficits in attention, processing speed, memory, and executive functioning as compared to healthy participants (Bearden et al., 2001; Depp et al., 2012; Robinson & Ferrier, 2006). Abnormalities persist in some domains during euthymic states, suggesting that individuals do not return to normal levels of cognitive functioning outside of acute mood episodes (Bearden et al., 2006; Bearden et al., 2001; Robinson et al., 2006). While cognitive deficits may partially reflect aspects of the disease like chronicity, evidence from first-degree relatives suggests cognitive dysfunction may be a neurally-mediated endophenotype of BD (Arts et al., 2009; Bora et al., 2009). Cognitive outcomes are important predictors of functioning and employment (Bearden et al., 2010; Depp et al., 2012; Martinez-Aran et al., 2004; Martino et al., 2009), pointing to potential clinical utility in better understanding cognitive profiles in BD.

Despite the large number of studies on neuropsychological functioning that have been conducted to date in BD, knowledge of how cognitive deficits unfold in the real world remains limited. Variables like acute mood and stress influence cognitive performance in healthy individuals (Chepenik et al., 2007; Curci et al., 2013; Klein & Boals, 2001; Schoofs et al., 2009; Sliwinski et al., 2009). Moreover, symptom severity and neuropsychological performance are related in individuals with unipolar depression (Antikainen et al., 2001; Lahr et al., 2007; Naismith et al., 2007) and BD (Dixon et al., 2003; Taylor Tavares et al., 2003). These studies raise the possibility that, in addition to stable, trait-like cognitive deficits that are observed in individuals with BD, there may be time-varying fluctuations in cognitive performance due to mood and situational factors, and these intraindividual cognitive variations may influence subjective well-being and functioning.

Most studies of cognitive performance in BD have used traditional neuropsychological measures assessed in a single sitting under quiet conditions in the laboratory or clinic. In contrast, mobile cognitive tools hold promise for ascertaining daily, and possibly fluctuating, cognitive performance deficits and their relationships to mood-related symptoms. Adaptations of cognitive tests for smartphones offer insights into the dynamic interaction of cognition with other environmental and affective variable and build upon the

analytic advantages offered by ecological momentary assessment methods (Ebner-Priemer et al., 2009). They provide valid estimates of cognitive performance and intraindividual variability that may provide useful information about clinical populations (Allard et al., 2014; Bouvard et al., 2018; Jongstra et al., 2017; Schweitzer et al., 2017; Sliwinski et al., 2018). In non-clinical samples, performance on mobile cognitive tests covaries with stress (Hyun et al., 2019) and mood fluctuations (Riediger et al., 2011; although see von Stumm, 2018). Moreover, individuals may endorse cognitive problems in daily life that do not emerge in a controlled testing environment. Thus, mobile cognitive tests may capture neuropsychological performance in a way that mirrors “real life”, as opposed to performance in sterile laboratory environments that is unlikely to reflect how an individual functions day-to-day (Moore et al., 2017). Given observed cognitive deficits and high intraindividual variability in mood observed in individuals with BD, this population may be particularly suited for assessment with ambulatory technologies.

This study reports data collected with our newly developed ecological momentary cognitive testing (EMCT) platform. In prior work, we reported the initial psychometric properties of this EMCT platform, including preliminary validity of seven mobile cognitive tests relative to laboratory-based (NIH Toolbox-Cognition Battery) neuropsychological performance (Moore et al., In Review). The current study expands the prior work, with a focus on examining the real-time and lagged relationships between mood and cognition. Specifically, in this study we explored both group level differences in mood and cognitive performance between individuals with BD and healthy volunteers (HV), as well as the real-time within-person relationships between mood and cognitive performance among individuals with BD. Four mobile cognitive tests were selected in an a priori manner based on the known relationships between the cognitive constructs measured (processing speed and working memory) and mood in people with BD. We hypothesized that individuals with BD would demonstrate worse average cognitive performance compared to HVs as measured by laboratory and mobile cognitive tests and that EMA ratings of non-euthymic mood would be associated with poorer cognitive performance within persons both concurrently and later the same day.

Methods

Participants

Participants were recruited with either (a) history of BD (n=46) or (b) no lifetime history of psychiatric diagnoses as healthy comparators (n=20). Participants were recruited via flyers in community centers (e.g., libraries and mental health clubhouses) and online recruitment portals (e.g., ResearchMatch, Studykik, and Craigslist). Inclusion criteria included: (i) diagnosis of BD on the MINI International Psychiatric Interview Version 6.0.0 (MINI; Sheehan et al., 1998) or no psychiatric diagnosis for healthy comparators, (ii) outpatient status, (iii) aged 18–65, (iv) fluency in English, (v) ability to provide written informed consent, and (vi) not on conservatorship. Exclusion criteria included: (i) a history of neurological disorder or head trauma with loss of consciousness >15 minutes, (ii) sensory impairment, (iii) substance use disorder in the past three months (excluding cannabis and tobacco), (iv) for the BD group, manic symptoms in the severe range as measured by a

score on the Young Mania Rating Scale (YMRS; >20; Young et al., 1978)) or depressive symptoms in the severe range as measured by the Montgomery-Asberg Depression Rating Scale (MADRS; >30; Montgomery & Åsberg, 1979), (v) suicidal ideation equal to or above a “Type 3” on the Columbia Suicide Severity Rating Scale (C-SSRS (Posner et al., 2011)) in the past month, (vi) concurrent enrollment in another research study.

Procedure

Procedures were approved by the UC San Diego Institutional Review Board, and all participants provided written informed consent. Participants completed a baseline visit including the MINI clinical interview used for eligibility determination, self-report questionnaires, and a neuropsychological battery. The MINI and neuropsychological battery were administered by bachelor’s level study staff who were trained to reliability standards and were supervised by a psychologist. Participants could use their own smartphone or borrow a study-provided Apple iPhone 7 to complete the EMCT protocol. Participants were trained on how to complete the mobile cognitive tests and participants completed one session of the EMCT protocol containing modified versions of seven cognitive tests (scores from four of which were analyzed in this study). Following the baseline visit, participants completed the EMCT protocol for 14 days. Participants received a mood survey and 2–3 mobile cognitive tests at three random times each day. Each mobile cognitive test was not administered more than once per day, and the order of administration was counterbalanced to ensure that each test was administered an equivalent number of times during the morning, midday, and early evening. Overall each mobile test was administered nine times. Timing intervals of EMCTs were adjusted according to each individual’s preferred sleep/wake schedule and there was a two hour minimum between each assessment so as to capture individual fluctuations in diurnal patterns. Further, adapting to the individual’s sleep/wake cycle was done to reduce the likelihood of data being influenced by variations in alertness which could lead time of day to impact testing performance. For example, if we administered the tests at preset times of 9:00am, 1:00pm, and 5:00pm for all participants, and participant A noted they go to sleep at 10:00pm and wake at 6:00am, while participant B stated they go to sleep at 3:00am and wake at 11:00am, participant B would never be awake for the first testing session. The software program, NeuroUX, pushes out weblinks of the mood surveys and mobile cognitive tests to participant’s phones, and the deidentified data are instantly uploaded to Amazon Web Services (AWS; HIPAA compliant), where it is accessible in real-time to study staff. To promote adherence and help trouble-shoot any difficulties, study staff contacted participants by telephone on the first day and if participants missed more than three surveys in a row. Participants were compensated for all study visits, and bonus compensation of \$1/survey was provided for each EMCT session completed.

Measures

Baseline Symptom Measures.—Participants with BD were assessed for depression using the interview-rated Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), with total scores ranging from 0–60 and higher scores indicating a greater severity (Müller et al., 2003). Symptoms of mania were assessed using the Young Mania Rating Scale (YMRS; Young et al., 1978), with a total score of 0–60 and higher scores indicating greater severity.

Baseline Cognitive Measures.—The NIH Toolbox Cognition Battery (NIH TB-CB) (Weintraub et al., 2013) assessed cognitive performance on one test each in the domains of language, episodic memory, attention, executive functioning, and processing speed. Age-corrected standard scores were used. Scores from all individual tests were averaged to create a Fluid Cognition score. The NIH TB-CB also includes a measure of literacy as an estimate of premorbid functioning and education (called the Crystallized Intelligence score).

Ecological Momentary Cognitive Testing (EMCT) Platform: EMA Survey.—Immediately prior to completion of the mobile cognitive tests, participants completed a survey designed to capture daily activities, social interactions and mood. EMA surveys were predominately presented in a check-box format. Affective states (happy, sad, energetic, relaxed, stressed) were measured on a scale from one to seven, with one indicating “not at all” and seven indicating “extremely.” For participants with BD, depression and mania were assessed categorically, with the options for the question “What is your current mood?” presented in the following manner: most ever manic, severe mania, moderate mania, mild mania, euthymic, mild depression, moderate depression, severe depression, and most ever depressed. These ratings were collapsed into three categories – depressed, manic, and euthymic – as participants could not report both depression and mania at the same time, but rather could only select one mood at a time on the scale. The percentage of surveys on which each category was endorsed was calculated.

Ecological Momentary Cognitive Testing (EMCT) Platform: Mobile Cognitive Tests.—The EMCT platform development was supported by a National Institute of Mental Health (NIMH) sponsored project (R21MH116104; PI: Moore). A human-centered design approach was applied to the development of the mobile cognitive tests (Lomas et al., 2017). Tests were gamified to increase engagement; gamification elements included a user-friendly interface structure, test playlist and scorecards, and optional gaming sounds (Lomas et al., 2017). Tasks were programmed to display different versions of stimuli at each administration. Prior to implementation, the platform was beta-tested in ten healthy comparators for usability, and refinements were made based on user feedback. In total, seven new mobile cognitive tests were developed, and data from four of these tests, measuring working memory, executive functions, processing speed, and reaction time are reported in this paper (Figure 1).

Matching Pair. Cognitive domain assessed: processing speed. Time to complete: 90 seconds.—In Matching Pair, participants were presented with a matrix of tiles with varying shapes of different colors. This tile matrix starts as a 2×2 size (4 tiles) and gradually increases to a maximum matrix of 4×4. Participants are asked to select the two matching shapes as quickly as possible, using one finger, to keep response method consistent. Scoring was calculated according to the grid size shown. The grid size was multiplied (e.g., 3×3=9) and added to the running score of the previously correct trial. For example, for a correct trial with a grid size of 4×4 and a previous trial score of 346, the trial score would be calculated as follows: 4×4=16; 16 + 346=a trial score of 362. If a trial response was incorrect, the score remained the same as the previously correct score. This

total score, which reflects a weighted sum of all correct trials, was recorded as measure of processing speed.

Memory Matrix. Cognitive domain assessed: visual working memory. Time to complete: variable; 3 trials; approximately 1–2 minutes (Mean completion time: 1.5 minutes).—In Memory Matrix, participants are presented with a matrix of tiles, starting with 2×2 and gradually increasing to a maximum of 7×7. A pattern of contrasting color tiles is presented to the participant and they are asked to memorize it. The contrasting pattern disappears and participants touch the tiles that were previously presented. The number of highlighted tiles increases by one for each correct response and decreases by one for incorrect responses, starting at one highlighted tile and proceeding to a maximum of 11 highlighted tiles. The task ends when three incorrect responses are made. Scoring was calculated according to correct responses on the number of highlighted tiles shown per trial. For each correct response, the number of highlighted tiles is added to the previously correct score. For example, if the previous trial score is 15 and a correct response was given on a trial with 6 highlighted cells, this trial's new score would be calculated as 21. If a trial response is incorrect, the score remained the same. This total score was recorded as a measure of working memory.

CopyKat. Cognitive domain assessed: visual working memory (primary); reaction time (secondary). Time to complete: variable; 3 trials, takes around 2–3 minutes (Mean completion time: 2.7 minutes).—Participants are presented with a 2×2 matrix of four different colored tiles: red, yellow, green, and blue. Tiles light up in a randomized sequence, and participants are asked to replicate the pattern after it is presented. The number of tiles that light up starts at one and increase incrementally by an n of one for each correct response, with no upper limit to the maximum number of tiles included in a sequence. When an incorrect response is made, the same sequence is presented again. The session ends after three incorrect responses (“trials”). Scoring was calculated by summing the number of correct trials. Incorrect responses are not penalized. This total correct response score was calculated as a measure of visual working memory. Reaction time was also recorded for each trial in seconds as a secondary cognitive domain.

Odd One Out. Cognitive domain assessed: working memory (primary); processing speed (secondary). Time to complete: variable; 9 trials, takes approximately 1 minute (Mean completion time: 0.75 minutes).—In Odd One Out, participants are presented with six symbols. They are asked to identify which symbol differs from the others as quickly as possible. For example, a trial may have five pictures of squares and one picture of a rectangle, with the rectangle being the correct response choice. There are a total of nine trials at each administration. Scoring was calculated by summing the number of correct responses, increasing by one for each correct response. Incorrect responses are not penalized. This total correct response score was calculated as a measure of working memory. Participants' response time on each trial in seconds was also recorded as a secondary domain of processing speed.

Statistical Analyses

Statistical analyses were performed using R (3.6.0) and SPSS v. 26. Descriptive statistics were used to examine participant characteristics, adherence, and overall laboratory and mobile cognitive test performance. To calculate overall mobile cognitive test performance, we used the median of participants' mobile cognitive test performance on each task across the 14 days. Independent samples t-tests were used to compare the BD and HV groups on demographic and usage variables as well as overall laboratory and mobile cognitive test performance. Linear mixed models were used to examine time of day impact on mobile cognitive test performance. We examined associations between baseline clinical variables (mood) and average cognitive performance using correlation analyses. Among participants with BD, linear mixed-effects models (R: lme4, lmerTest) were used to analyze within-person relationships between mobile cognitive test performance and mood with alpha set to $p < .01$ to adjust for multiple comparisons. Analyses were performed concurrently, i.e., indicating the contemporaneous relationships between mood and mobile cognitive test performance, and lagged, seeing how previous survey mood related to next survey mobile cognitive test performance (only same-day lagged analyses performed). We first ran a model only with the mood variable(s) predicting mobile cognitive test performance, and then as a second iteration of the model controlling for age, gender, race, and years of education. Lagged analyses included current survey mood as a covariate in all iterations of the model. Concurrent and lagged models, both with and without covariates, were run separately for each of the 6 cognitive test scores. Clinical mood states (depression, mania) were entered into a regression, and performance during these mood states were compared to performance during euthymia. Other emotion variables were examined continuously. We also examined associations between variability in mood ratings using mean squared successive difference (MSSD), which measures the variability of trial by trial observations in addition to overall between-trial variation. Examination of relationships between MSSD and cognitive performance on mobile tests were conducted using correlation analyses with alpha set to $p < .01$ to adjust for multiple comparisons.

Results

Participants were well matched on demographic variables (p 's $> .205$, Table 1). Participants with BD were more likely to be unemployed than healthy controls (Table 1). On laboratory cognitive tests, participants had lower scores on executive functioning and episodic memory tests. There were no other statistically significant differences in scores between participants with BD and HVs, with mean scores from both groups falling in the average range. There were no significant relationships between baseline mood and neuropsychological assessments (see Table 2).

Adherence to the EMCT protocol was generally high and similar between the two groups (72.97% completion of the 42 EMCT sessions in the BD group vs. 78.59% in the HV group; $t(64)=1.00$, $p=.161$; Table 1). Using aggregate EMA data over the 14-days, individuals with BD reported lower energy ratings than HVs ($t(62)=-3.69$, $p < .001$) as well as higher sadness than HVs ($t(62)=3.99$, $p < .001$; Table 1). Individuals with BD were more variable in ratings of happiness and sadness relative to HVs (Table 1). Participants with BD reported

depressed mood more frequently than manic or euthymic mood (Table 1). In the BD group, baseline MADRS scores correlated with percentage of time reported depressed on EMA ($r(44)=.49, p<.001$) and baseline YMRS scores correlated with percentage of time reported manic on EMA ($r(44)=.47, p<.001$). Though statistically non-significant, participants with BD performed slightly worse on mobile cognitive tests than HVs, with the biggest non-significant effect sizes in domains of processing speed (Matching Pair Total Score Cohen's $d=0.51, p=.076$) and visual working memory (Memory Matrix Cohen's $d=0.57, p=.052$; Odd One Out Score Cohen's $d=0.58, p=.049$; Table 3). Linear mixed models revealed that time of day had a significant but small impact on some mobile cognitive tests, but not others. Time of day did not significantly impact Memory Matrix, Matching Pairs, or Copy Kat Score (p 's $>.05$). However, it had a significant but small impact on Copy Kat Response Time ($b=0.001, S.E.=0.0004, t=2.45, p=.015$), Odd One Out score ($b=-.0003, S.E.=0.0001, t=-2.24, p=.026$), and Odd One Out response time ($b=0.0003, S.E.=0.00008, t=3.94, p<.001$).

Depression and Mania-Mobile Cognitive Test Relationships.

There were no significant correlations between baseline depression or mania and mobile cognitive test scores ($ps>.020$; Table 4). Mixed effects regression results revealed one set of significant within-person relationships between mobile mood and mobile cognitive test performance among participants with BD. Previous survey mania predicted poorer performance on the Odd One Out response time (measuring processing speed [PS]) compared to euthymic mood ($estimate=1.57, SE=.33, p<.001$). This remained significant when controlling for current survey mood and demographic covariates ($estimate=1.5, SE=.32, p<.001$; Figure 2).

EMA Negative Affect/Energy-Mobile Cognitive Test Relationships.

There were no statistically significant concurrent or lagged effects of energetic ratings with any of the mobile cognitive tests. Intra-individual variance in energy ratings was correlated with Matching Pair score ($r=-.38, p=.008$). Higher previous survey sadness ratings related to higher Memory Matrix total score (Visual Working Memory (WM); $estimate=1.19, SE=.45, p=.009$), which remained significant when controlling for current survey sadness, age, gender, race, and years of education ($estimate=1.14, SE=.45, p=.013$). Furthermore, higher concurrent stress ratings were related to better Odd One Out total score (working memory (WM); $estimate=.10, SE=.04, p=.007$), which remained significant when controlling for age, gender, race, and years of education ($estimate=.10, SE=.04, p=.010$).

EMA Positive Affect-Cognition Relationships:

Higher happiness ratings also related to better concurrent performance on Matching Pair total score (PS; $estimate=11.7, SE=3.29, p<.001$), which remained significant when controlling for age, gender, race, and years of education ($estimate=10.5, SE=3.19, p=.001$). No significant effects were observed for relaxed ratings.

Discussion

The current study utilized a newly-developed EMCT platform to elucidate relationships between affective variables and real-world cognitive performance in individuals with BD. In BD compared to HVs, cognitive performance was slightly worse and more heterogeneous on both laboratory-based cognitive tests and mobile cognitive tests in specific domains. Performance on traditional cognitive tasks was not associated with baseline clinical ratings of depressive or manic symptom severity. As expected, individuals with BD rated lower energy and greater sadness relative to HVs on mobile surveys; similarly, among BD, the median percentage of surveys with depressed mood endorsed was 24%, compared to 3% for manic mood, and 61% for euthymia. The BD group had more variable happy and sad ratings than the HV group. Among the BD group, prior mood ratings differentially related to cognition, such that prior mania was related to worse processing speed (Odd One Out time) but prior sadness was related to better visual working memory performance (Memory Matrix score). In contrast, concurrent ratings of elevated happiness related to better processing speed (Matching Pair score), while greater stress related to better working memory performance (Odd One Out score). While few relationships were observed with MSSD, variance in energy ratings was correlated with Matching Pair scores. Not all mood ratings or cognitive domains were related, suggesting variability in test sensitivity or that some affective states may not influence cognitive performance in people with BD.

Capturing interrelationships as they unfold temporally provides a nuanced picture that could be missing in a laboratory-based “snapshot.” For example, the current data revealed a positive association between current happiness and processing speed, which may suggest that real-time emotions characterized by high arousal can enhance certain types of cognitive performance. This proposal is consistent with numerous prior studies showing that positive emotion enhances external attention processes (Carver, 2003; Tamir & Robinson, 2007). However, prior mania related to subsequently lower reaction time processing speed performance that was not captured in the concurrent testing relationships. These data point to a potential cognitive cost of manic symptoms that unfolds over time, akin to prior descriptions of the adverse effects of “too much” positive emotion (Gruber et al., 2011; Oishi et al., 2007). Thus, high arousal positive emotion may be beneficial for processing speed but only to a certain extent. In the absence of repeated testing, distinguishing the current versus future effects of these positively valenced mood states would not be possible.

In the case of negatively valenced emotions, ratings of stress and sadness both were associated with better working memory, which is at odds with prior literature suggesting that negative emotion adversely affects this cognitive domain (Curci et al., 2013). Methodological reasons might account for divergence in findings. Studies of mood-cognition relationships have historically relied on laboratory-based mood inductions, rather than measuring naturalistic fluctuations over time, because of the lack of available real-time testing tools like those used in our study. Another possible account of this data is that individuals experiencing negative emotion recruit cognitively-based emotion regulation strategies in an attempt to modulate their mood. Given that cognitive emotion regulation (e.g., reappraisal) is strongly rooted in systems shared with working memory (Schmeichel et al., 2008), one hypothesis is that bringing these cognitive resources “online” may have

a beneficial effect on cognitive testing. An alternative explanation is that individuals with BD differentially recruit neural systems in reaction to negative mood, leading to a pattern of mood-working memory relationships different from that observed in healthy participants. For example, data indicates that individuals with BD demonstrate increased activation in prefrontal regions during working memory in response to a sad mood induction, while healthy participants do not (Deckersbach et al., 2008). Furthermore, due to the convergence of the Odd One Out task with laboratory-based neuropsychological working memory tests (Moore et al., in review), and the correlation of fluid reasoning and working memory tasks while under time pressure (Chuderski, 2013), we chose to label this test as working memory rather than fluid reasoning. Future research will be needed to clarify the underlying mechanisms of negative mood-related working memory and fluid reasoning changes in this group.

Dynamic cognitive deficits in the context of mood changes have the potential to significantly impede successful occupational and social functioning in BD. A growing body of work reveals that processing speed significantly impacts daily functioning in diverse clinical disorders including schizophrenia (Costa et al., 2016; Ojeda, Pena, et al., 2012; Ojeda, Sanchez, et al., 2012). Processing speed deficits likely influence functioning across cognitive domains (e.g., learning, executive function; (Chiaravalloti et al., 2003), and may interfere with skill development and comprehension of complex instructions necessary for complex tasks. Understanding how these affect-related changes in processing speed emerge in daily life may thus provide clinically useful information (e.g., planning for situations that may impact following through with treatment recommendations). More data is needed to understand how specific cognitive profiles emerge within individuals with BD, including whether some individuals are particularly susceptible to cognitive decreases in the face of affective shifts. Further, we found small but significant impact of time of testing on some of the mobile cognitive tests, and further work with larger samples is needed to more comprehensively explore the impact of time of day, in conjunction with sleep patterns and routines, on cognitive performance.

The study has several limitations. First, the sample collected was relatively small in size. The nature of the small sample may increase the potential of Type II error, whereby effects with a sizeable magnitude (such as the between group cognitive differences) do not meet our statistical threshold. A larger study will be needed to replicate results and ensure robustness with multiple comparison corrections. In addition, a larger dataset will permit more detailed examination of patient-level moderators that are important for cognitive functioning, such as medication usage. The mood ratings used may have insufficiently captured affective states because when individuals were actually in that mood state, insight could be diminished. While use of single item ratings is optimal for brief EMA assessments, it may also reduce the ability to infer which aspect of the mood state may impact cognitive performance. The extent to which timing impacts the observed relationships warrants additional study. Future work is needed to examine whether things like device factors (e.g., screen size) have an impact mood-cognition relationships. The BD group did not reflect the full spectrum of mood severity and was generally a highly educated sample. We did not evaluate the effects of variables like chronicity in our models. Thus, future work will be helpful in mapping relationships between affective variables and cognition in a largely representative sample. A

comprehensive assessment of long-term functional outcomes was not collected, which limits our ability to predict clinically-meaningful outcomes from the EMA measurement burst. Further data collection is also needed expand on the initial psychometrics data obtained on the tests in a larger sample of control participants as well as in other clinical populations.

Despite these limitations, we observed significant associations between affective variables and working memory and processing speed in BD. One advantage of the EMCT platform is its portability. Attending in-person laboratory assessments may pose a challenge for individuals due to feasibility (e.g., requiring travel in rural communities) such as has been acutely highlighted by the COVID-19 pandemic. Availability of a platform that can provide neuropsychological assessment using commonly available smartphone technologies could thus be clinically advantageous. Findings support the use of mobile cognitive testing as a tool for understanding links between shifts in mood and real-world cognitive performance, and may inform our understanding of how subtle real-time shifts relate to important functional and clinical outcomes.

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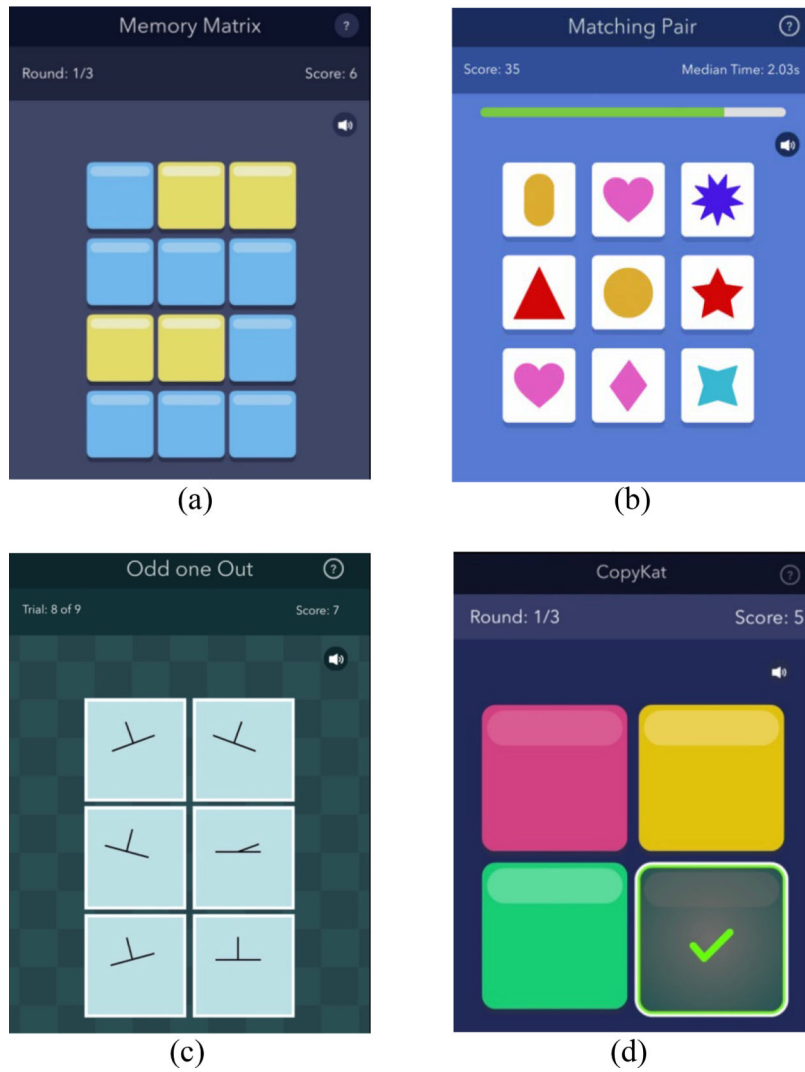


Figure 1. Screen shots of four newly developed mobile cognitive tests: (a) Memory Matrix, (b) Matching Pair, (c) Odd one Out, and (d) CopyKat.

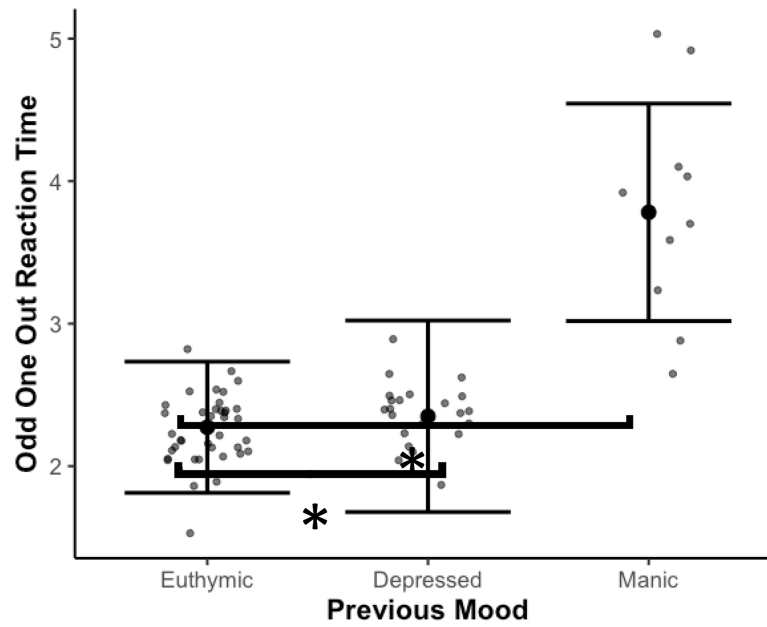


Figure 2. Mobile cognitive testing performance on a) matching pairs and b) odd one out by mood state. Figure illustrates linear mixed effects models with concurrent or previous mood related to mobile cognitive performance. Previous mood indicates that previous-survey mood ratings were related to current survey mobile cognitive performance. *Note.* Only participants with BD included.

Table 1.

Demographics, Clinical Characteristics, Cognition, and EMA Aggregate Mood

| | BD (N=46) | HV (N=20) | T or X² | p |
|--|--------------------------|--------------------------|---------------------------|----------|
| Age; years; M(SD); Range | 42.7 (11.4); 19.6 – 61.3 | 41.0 (14.6); 18.6 – 65.4 | 0.503 | .617 |
| Sex (% F) | 65.2% | 70% | 0.009 | .925 |
| Race (%) | | | 7.22 | .205 |
| White | 54.4% | 35% | | |
| Black/African American | 8.7% | 10% | | |
| Asian | 4.3% | 25% | | |
| Other | 32.6% | 30% | | |
| Ethnicity (% Hispanic or Latino) | 17.3%* | 10% | 0.18 | .667 |
| Education; years; M(SD) | 14.9 (2.6) | 15.7 (2.7) | -1.06 | .292 |
| Employment Status | | | 12.51 | .006 |
| Unemployed | 50% | 5% | | |
| In school | 2.2% | 5% | | |
| Part time employment | 19.6% | 30% | | |
| Full time employment | 28.3% | 60% | | |
| Residential Status | | | 0.93 | .819 |
| Independent, financially responsible | 78.3% | 80% | | |
| Independent, not financially responsible | 17.4% | 20% | | |
| Unsupervised residential facility | 2.2% | 0% | | |
| Supervised residential facility | 2.2% | 0% | | |
| Income | | | 8.3 | .016 |
| <\$19,000 | 61% | 21.1% | | |
| \$20,000–74,999 | 29.3% | 57.9% | | |
| >\$75,000 | 9.8% | 21.1% | | |
| Clinical Characteristics | | | | |
| Substance Use | | | | |
| Alcohol | | | 3.40 | .183 |
| Abstinent | 45.7% | 30% | | |
| Infrequent-moderate | 47.8% | 70% | | |
| Heavy or very heavy | 6.5% | 0% | | |
| Cannabis | | | 7.38 | .194 |
| Current abuse | 4.3% | 0% | | |
| Current dependence | 4.3% | 0% | | |
| Former use disorder | 15.2% | 0% | | |
| Other | | | 9.55 | .023 |
| Current abuse | 0% | 0% | | |
| Current dependence | 0% | 0% | | |

| | BD (N=46) | HV (N=20) | T or X² | p |
|---|------------------------|-------------------------|---------------------------|----------|
| Former use disorder | 26.1% | 0% | | |
| MADRS | 11.2 (8.5) | N/A | N/A | N/A |
| YMRS | 6.4 (5.6) | N/A | N/A | N/A |
| Current Medications | | | | |
| Mood Stabilizers | 54.3% | 0% | 17.50 | < .001 |
| Antipsychotics | 45.7% | 0% | 13.39 | < .001 |
| Antidepressants | 45.7% | 0% | 13.39 | < .001 |
| NIH Toolbox (Baseline Cognition; Age Corrected Standard Score): M(SD); Range | | | | |
| Total Fluid Intelligence | 97.2 (19.8); 59 – 146 | 106.9 (11.2); 85 – 132 | -2.51 | .015 |
| Total Crystallized Intelligence | 104.6 (14.5); 68 – 127 | 105.2 (14.6); 68 – 129 | -0.17 | .870 |
| Flanker Inhibitory Control and Attention | 91.4 (15.4); 67 – 133 | 93.6 (10.5); 69 – 122 | -0.69 | .495 |
| Dimensional Change Card Sort Test | 100.8 (20.3); 58 – 146 | 109.9 (12.0); 88 – 128 | -2.27 | .027 |
| Pattern Comparison Processing Speed Test | 102.6 (20.9); 59 – 146 | 109.4 (17.5); 78 – 146 | -1.27 | .210 |
| List Sorting Working Memory Test | 97.4 (15.5); 56 – 129 | 104.25 (12.6); 73 – 124 | -1.73 | .088 |
| Picture Sequence Memory Test | 99.0 (17.4); 74 – 141 | 106.6 (12.2); 79 – 129 | -2.02 | .049 |
| EMA Adherence and Aggregated Mood Rating | | | | |
| Surveys Completed, % | 72.97% | 78.59% | 1.00 | .161 |
| Median Percentage of Surveys Depressed | 24% | 0% | 163.5 [±] | < .001 |
| Median Percentage of Surveys Manic | 3% | 0% | 360 [±] | .132 |
| Median Percentage of Surveys Euthymic | 61% | 98% | 774 [±] | < .001 |
| “Energetic” Mean Rating; M(SD) | 3.19 (0.98) | 4.22 (1.13) | -3.69 | < .001 |
| MSSD | 3.05 | 2.38 | -1.93 | .297 |
| “Relaxed” Mean Rating; M(SD) | 4.04 (1.00) | 4.50 (1.05) | -1.67 | .100 |
| MSSD | 2.44 | 2.58 | 0.27 | .785 |
| “Sad” Mean Rating; M(SD) | 2.81 (1.28) | 1.58 (0.79) | 3.99 | < .001 |
| MSSD | 1.9 | 0.79 | 3.23 | .002 |
| “Happy” Mean Rating; M(SD) | 4.20 (1.11) | 4.85 (1.17) | -2.17 | .034 |
| MSSD | 2.04 | 1.17 | -2.12 | .038 |

Note. BD=bipolar disorder; HV =healthy volunteers; MADRS=Montgomery-Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale; NIH=National Institute of Health; EMA=Ecological Momentary Assessment; MSSD= mean squared successive deviation

* N=1 missing (participant not willing to provide)

[±] Indicates Mann-Whitney U test used

Table 2.

Pearson Correlations between Baseline Mood and Baseline Cognition (NIH Toolbox); N=46, BD Sample Only

| | MADRS | YMRS |
|---|---------------------|----------------------|
| Total Fluid Intelligence | .167 ($p = .267$) | -.084 ($p = .577$) |
| Total Crystallized Intelligence | .162 ($p = .281$) | -.007 ($p = .966$) |
| Flanker Inhibitory Control and Attention Test | .057 ($p = .708$) | -.107 ($p = .478$) |
| Dimensional Change Card Sort Test | .141 ($p = .348$) | .004 ($p = .978$) |
| Pattern Comparison Processing Speed Test | .152 ($p = .315$) | -.143 ($p = .343$) |
| List Sorting Working Memory Test | .091 ($p = .547$) | -.024 ($p = .875$) |
| Picture Sequence Memory Test | .156 ($p = .302$) | -.039 ($p = .799$) |

Note. BD=Bipolar Disorder; MADRS=Montgomery-Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale

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Table 3.

Aggregate Median Mobile Cognitive Test Performance – Median (SD)

| | BD (n=46) | HV (n=20) | Cohen's D | T | p |
|--|------------------|------------------|------------------|----------|----------|
| Matching Pair (Processing Speed; Total Score) | 285.7 (91.3) | 327.2 (71.6) | 0.51 | -1.80 | .076 |
| Memory Matrix (Visual Working Memory; Total Score) | 39.3 (12.0) | 45.2 (8.4) | 0.57 | -1.98 | .052 |
| CopyKat (Visual Working Memory; Total Score) | 9.1 (3.2) | 9.9 (2.4) | 0.29 | -1.04 | .303 |
| CopyKat (Reaction Time; # Seconds) | 9.0 (2.7) | 9.2 (2.6) | 0.13 | -0.49 | .627 |
| Odd One Out (Working Memory; Total Score) | 8.2 (0.8) | 8.6 (0.5) | 0.58 | -2.01 | .049 |
| Odd One Out (Processing Speed; # Seconds) | 2.4 (1.0) | 2.1 (0.5) | 0.37 | 0.99 | .328 |

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Table 4.Mobile Cognitive Test Correlations with Depression and Mania – Pearson's *r*

| | MADRS Score | YMRS Score |
|--|-------------------------|--------------------------|
| Matching Pair (Processing Speed; Total Score) | 0.117 (<i>p</i> =.440) | -0.097 (<i>p</i> =.522) |
| Memory Matrix (Visual Working Memory; Total Score) | 0.035 (<i>p</i> =.817) | -0.146 (<i>p</i> =.340) |
| CopyKat (Visual Working Memory; Total Score) | 0.346 (<i>p</i> =.020) | 0.036 (<i>p</i> =.816) |
| CopyKat (Reaction Time; # Seconds) | 0.263 (<i>p</i> =.084) | -0.080 (<i>p</i> =.604) |
| Odd One Out (Working Memory; Total Score) | 0.202 (<i>p</i> =.184) | -0.076 (<i>p</i> =.619) |
| Odd One Out (Processing Speed; # Seconds) | 0.015 (<i>p</i> =.924) | 0.217 (<i>p</i> =.152) |

Note. MADRS=Montgomery-Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale

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