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Journal

Bipolar Disorders, 22(1)

ISSN

1398-5647

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Publication Date

2020-02-01

DOI

10.1111/bdi.12786

Peer reviewed

HHS Public Access

Author manuscript

Bipolar Disord. Author manuscript; available in PMC 2021 February 01.

Published in final edited form as:

Bipolar Disord. 2020 February ; 22(1): 46–58. doi:10.1111/bdi.12786.

Convergent neural substrates of inattention in bipolar disorder patients and dopamine transporter-deficient mice using the 5-choice CPT

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Abstract

Objectives: Bipolar disorder (BD) is a debilitating psychiatric illness affecting 2–5% of the population. Although mania is the cardinal feature of BD, inattention and related cognitive dysfunction are observed across all stages. Since cognitive dysfunction confers poor functional outcome in patients, understanding the relevant neural mechanisms remains key to developing novel targeted therapeutics.

Methods: The 5-choice continuous performance test (5C-CPT) is a mouse and fMRI-compatible human attentional task, requiring responding to target stimuli while inhibiting responding to non-target stimuli, as in clinical CPTs. This task was used delineate systems-level neural deficits in BD contributing to inattentive performance in human subjects with BD as well as mouse models with either parietal cortex (PC) lesions or reduced dopamine transporter (DAT) expression.

Results: Mania BD participants exhibited severe 5C-CPT impairment. Euthymic BD patients exhibited modestly impaired 5C-CPT. High impulsivity BD subjects exhibited reduced PC activation during target and non-target responding compared with healthy participants. In mice, bilateral PC lesions impaired both target and non-target responding. In the DAT knockdown mouse model of BD mania, knockdown mice exhibited severely impaired 5C-CPT performance versus wildtype littermates.

Conclusions: These data support the role of the PC in inattention in BD – specifically regarding identifying the appropriate response to target versus non-target stimuli. Moreover, the findings indicate that severely reduced DAT function/hyperdopaminergia recreates the attentional deficits observed in BD mania patients. Determining the contribution of DAT in the PC to attention may provide a future target for treatment development.

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Keywords

Vigilance; parietal cortex; lesion; gene; mania; attention

INTRODUCTION

Bipolar disorder (BD) is a life-long debilitating psychiatric illness affecting 2–5% of the population (1), with patients spending ~10–12% of time in a hypomanic/manic state, the defining feature BD (2). Although BD is characterized by complex and multifaceted symptoms including elevated mood, patients who show cognitive deficits have poorer functional outcome (3). One dominant symptom of BD is inattention (4), recognized as core to cognitive deficits across psychiatric conditions (5, 6). The development of pro-attentive therapies will likely lead to more generalized cognitive improvement. Unfortunately, no targeted pro-attentive treatments have been established (7–9), in part due to our limited understanding of the neural systems underlying this deficit.

The neurobiology underlying impaired attention in BP remains to be elucidated. Recent research has found participants with BD exhibit altered parietal cortex (PC) activation during attentional testing (10), in a continuous performance test (CPT), as do individuals at increased genetic risk for either schizophrenia or BD (11, 12). More specifically, right fronto-PC dysfunction may underlie spatial attentional deficits in BD patients (13), which may also relate to impaired performance on flexible decision-making (14), and cognitive control tasks (15). The neurobiology underlying these deficits beyond regional localization remains unclear.

While studying the human brain with neuroimaging is one important tool in psychiatry research, regional and systems neurotransmitter specificity can best be tested with experimental manipulations such as lesions or genetic modification in cross-species studies. To explore the neurobiology of attentional deficits, we examined 5-choice (5C-)CPT performance in mice with reduced DAT functioning (knockdown; KD), which exhibit numerous behaviors consistent with BD mania including hyperactivity, increased specific exploratory profiles, and straighter-line movements in the cross-species behavioral pattern monitor (16–18), as well as risk-taking in the Iowa Gambling Task (19, 20). Additionally, mouse studies enable determining the contribution of the PC to mouse 5C-CPT performance, given its potential importance for attention in humans.

We developed the 5C-CPT for use in mice and rats (21–26). Unlike other rodent attentional tasks, the 5C-CPT includes target and non-target trials requiring a response or the inhibition of response respectively (Fig. 1A), consistent with human CPTs. Hence, the 5C-CPT similarly quantifies the hit rate (responding to targets), false alarm rate (responding to non-targets), and d-prime (the difference scores signifying overall attention) of participants, as can the traditional accuracy measure (lit vs. unlit aperture responses) from the 5-choice serial reaction-time task (5-CSRTT; Supplemental Figure 1A). Construct and predictive validity for the 5C-CPT is seen wherein 36-hour sleep deprivation similarly impairs, while amphetamine treatment similarly improves 5C-CPT performance respectively in humans and mice (27, 28). Reverse-translation of this task for humans revealed PC activation during

functional magnetic resonance imaging (fMRI) performance (29). Here, using cross-species studies, we determined whether the PC contributes to human and mouse 5C-CPT performance and whether reduced DAT functioning would recreate attentional deficits of people with BD.

METHODS AND MATERIALS

Human Participants

Participants with bipolar mania and healthy controls—Male and female acutely hospitalized participants with SCID (Structured Clinical Interview for DSM-IV) diagnosed DSM-IV Bipolar Disorder, Current Episode Mania, plus healthy volunteers who had never met criteria for an Axis I Disorder as determined by SCID, recruited from the community, between 18–55 years old, participated in this study (n=9 and 13 respectively; see Table 1 also for demographic and illness factors). Participants were excluded if they had abused or been dependent on alcohol or substances within the past month, had a positive result on a urine toxicology screen, had a neurological condition, or had a condition that impaired motor functioning.

All BD mania patients were prescribed psychotropic medication during the time of testing and were typically treated with a combination of mood-stabilizing and atypical antipsychotic medications. The most common antipsychotic medication prescribed was risperidone, and the most common mood stabilizers prescribed were lithium and valproate. After consenting to the study, the Brief Psychiatric Rating Scale (BPRS) (30) and the Young Mania Rating Scale (YMRS) were administered, participants were considered manic if they met a YMRS score >13. Participants were then tested in the 5C-CPT.

Participants with euthymic bipolar disorder and healthy controls without fMRI —Female and male participants (BD n=40, healthy participants n=55), were tested as part of a larger study of brain aging in bipolar disorder. Inclusion criteria for patients were as follows: patient must be between the ages of 30 and 79, right handed, free from substance abuse for 6 months and substance dependence for 12 months, suitable for MRI (i.e., no implanted medical devices), a native English speaker and may never have been diagnosed with a serious neurological or medical condition. Comparison participants were free of any Axis I diagnoses and did not have first-degree relatives with BD or schizophrenia. These participants did not overlap with those in our previous study (30), whose results were used to create regions of interest for the analysis. BD patients met DSM-IV criteria for bipolar I disorder, were on stable doses of medication for at least 6 weeks, and reported their first mood episode as occurring between the ages of 13 and 30. BD patients were also excluded from the study if they were experiencing a mood episode or had a history of any other Axis I DSM-IV diagnosis. The expanded version of the SCID-IV was administered to all BD patients. Participants were considered euthymic if they met cutoff scores on the Hamilton Depression Rating Scale [HAM-D ≤7; (31)], the YMRS (≤6; (32)], and the Positive and Negative Syndrome Scale [PANSS positive≤21 and PANSS negative≤21; (33)]. Comparison participants were administered the Mini International Psychiatric Interview (34). Table 2 provides demographic information.

Participants with euthymic bipolar disorder and healthy controls with fMRI scanning—BD participants (n=27) were clinically stable on the same dose of medication for the past six weeks, did not have recent history of drug or alcohol dependence, and were free of other Axis I diagnoses. Most were scanned in a confirmed euthymic state because they were participants in the above-described study (out of scanner); for 5 participants, mood state was not confirmed. Healthy comparison participants without current or past diagnosis of mental illness (n=10) were also scanned. All participants were right handed. Table 3 provides demographic information.

Animal Subjects

Male C57BL/6J mice (n=24) were 6 months old at the time of testing and weighed between 20–28 g. DAT heterozygous mice backcrossed onto a C57BL/6 background originally generously donated from the University of Chicago (35), were bred to produce male WT (n=28) and KD (n=31) littermate mice, which were trained and tested in the 5C-CPT at approximately 5–6 months of age. All animals were group housed (maximum 4/cage) and maintained in a temperature-controlled vivarium (21±1 °C) under a reversed day-night cycle (lights on at 7:00 PM, off at 7:00 AM). All testing occurred during the dark phase of the day-night cycle between 9:00 AM and 14:00 PM. Mice had *ad libitum* access to water and were food-restricted at 85% of their free-feeding weight during training and testing. All procedures were approved by the UCSD Institutional Animal Care and Use Committee. The UCSD animal facility meets all federal and state requirements for animal care and was approved by the American Association for Accreditation of Laboratory Animal Care.

Mouse 5-CSRTT and 5C-CPT

DAT knockdown mice were initially trained in the 5CSRTT and compared to wildtype littermates (36, 37), with C57Bl/6J and DAT knockdown male mice then trained in the 5C-CPT (38). Once trained and stable, C57Bl/6J mice were subjected to bilateral PC lesions (n=15) or sham treatments (n=9) and retrained/tested in the 5C-CPT after recovery from surgery. See Fig. 1A for the task schematic (26, 39). In brief, mice were first trained to associate reward with entry to the delivery area in a fixed interval 15 s (2 sessions). Mice were then trained to respond to 1 of 5 lit apertures to receive the same reward (fixed ratio 1 until >60 responses were made for 2 consecutive days, approximately 14 sessions). Mice were then required to make a holepoke if 1 of the 5 holes lit up (target trials, 20 s stimulus duration) in order to obtain a food reward (Hit). Responding to an unlit hole resulted in a timeout (Incorrect). Failure to respond during target trials resulted in a timeout (Miss/omission). Responding before any stimuli appeared resulted in a timeout (premature response). Training continued until stimulus duration was 2 s (from 20, 10, 8, 4, then 2 s after meeting criterion of >20 correct trials with a mean correct latency < half the current stimulus duration). The performance of the mice at this time was recorded as their 5-CSRTT performance. Mice were then trained to inhibit from responding in the 5C-CPT. Inhibition of responding was required when all 5 holes lit up (non-target trials) was also rewarded (Correct Rejection; CR), while responding to these stimuli resulted in a timeout (False Alarm; FA). Training continued until performance was stable on d prime, % omissions, and RTs when tested for baseline performance over 3 days before baseline-matching prior to PC

lesion studies. Several measures were determined from this task and calculations based on hit rates (HR), FA rates (FAR), were made accordingly:

$$Accuracy = \frac{Hit}{Hit + Incorrect}$$

$$\%\ Omissions = \left(\frac{Miss}{Total\ Trials}\right) \times 100$$

$$Reaction\ Time = \frac{Cumulative\ Correct\ Latency}{Corrects}$$

$$HR = \frac{Hit}{Hit + Miss} \qquad FAR = \frac{FA}{FA + CR}$$

Signal detection indices were calculated based upon these basic parameters to assess both sensitivity and responsivity indices:

$$d\ prime = z(HR) - z(FAR) \qquad RI = \frac{HR + FAR - 1}{1 - [FAR - HR]^2}$$

d prime provides a parametric assessment of sensitivity to appropriate responding. The non-parametric response bias measure RI provides a measure of the 'tendency to respond'. Low numbers indicate a conservative response strategy, while high numbers indicate liberal responding (40, 41).

Parietal Cortical Lesion study

Once training was completed, the mice were injected with bilateral intracerebral infusions of ibotenic acid to lesion the parietal cortices (42). The Supplemental Methods provide the detailed protocol.

Human 5C-CPT apparatus

The task appeared on a 56 cm CRT computer screen (60 cm from participant). Human participants used an arcade joystick to make responses. The joystick was spring-mounted so that it would return to the center after each response, responding to target stimuli in the indicated direction (single circle; Fig. 2A) or inhibiting to non-target stimuli (all 5 circles; Fig. 2B). Calculations of performance was consistent with the mouse 5C-CPT. A Dell PC with E-Prime2 software (Psychology Software Tools) was used for stimulus presentation and data acquisition. Supplemental Methods provide the detailed protocol.

fMRI Scanning Methods

Human 5C-CPT for Imaging Study—Task parameters were similar to the above (see Supplemental Methods for more detail); participants viewed the images projected on a

screen at their feet through a mirror on the headcoil and an MRI-compatible joystick was used. There was a ratio of 5 to 1 target versus non-target trials with a total of 120 target trials and 24 non-target trials across four runs of the task. Blocks of fixation trials and task trials of 30 s duration each were interspersed. Each run consisted of 11 blocks and lasted for 5 min and 10 s. A total of four runs were collected for each participant.

Imaging Study Procedure and Processing—Functional magnetic resonance imaging was conducted on a 3T GE Signa EXCITE whole-body scanner with the following parameters: TR=2000 ms, TE=30 ms, image matrix=64×64, 4×4 mm resolution, 30 slices. Field map correction for scanner inhomogeneities was applied. AFNI software was used to correct images for motion, align with the anatomical scan, and apply spatial blurring. The degree of response during correct target and correct non-target trials was estimated separately using each participant's behavioral data to create individual reference functions. A general linear model (GLM) was applied with predictors to account for drift and motion as well as gamma-function-convolved reference functions for correct target and non-target trials. Individual GLM maps for target and non-target trials were then transformed into standard space for group analyses. Before scanning, seventeen of the BD patients also completed the Positive Urgency Measure (PUM) scale (43), which assesses self-report of the degree of impulsivity during positive mood states.

Statistical analysis for out of scanner behavioral studies—After confirming homogeneity of variance, primary outcome variables were analyzed using a one- or two-way analysis of variance (ANOVA). Human 5C-CPT data were analyzed using mixed factor ANOVAs with population and gender as the between- and trial block as the within-subjects factors. Mouse 5C-CPT data were analyzed using mixed two-way ANOVAs with genotype or lesion group as between- and trial block as within-subjects factors. Statistically significant main or interactive effects were subjected to further analyses using one-way ANOVAs and/or Tukey *post hoc* comparisons. All data were analyzed used SPSS 24.0 (Chicago, IL.) and represented by mean and standard error of the mean. Alpha level was set to 0.05.

Imaging study statistical analysis—Given concerns about cluster-wise inference in fMRI data (44), we used an *a priori* region of interest (ROI) approach. Clusters of brain response reported for an independent sample of healthy individuals (n=10) in our previous paper (21), were used as ROIs. The mean fit coefficient for target and non-target response within each of 6 target and 6 non-target ROIs was calculated. Single sample t-tests were conducted within each group to verify a response significantly above zero in each ROI. Then, independent sample t-tests were conducted to examine group differences in response, while accounting for group differences in age and education [healthy control (HC) participants were older and less educated]. Within the BD group, correlation of ROI response with scores on the PUM scale was assessed in a subsample of 17 individuals.

RESULTS

Parietal cortex lesion effects on rodent 5-CSRTT and 5C-CPT

Over the 6 days following PC or sham lesions, main performance improved as measured by increased hit rate ($F_{(6,120)}$=7.0, p<0.0001), lower false alarm rate ($F_{(6,120)}$=3.1, p<0.01), faster reaction-times ($F_{(6,120)}$=2.9, p<0.05), reduced motoric impulsive responses ($F_{(6,120)}$=6.4, p<0.001), modest alterations in accuracy ($F_{(6,120)}$=2.5, p<0.05), and increased d prime ($F_{(6,120)}$=3.6, p<0.005). Total trials did not increase over time (F<1, ns). Bilateral PC lesions were confirmed (Fig. 1B).

Attentional improvement over time was largely driven by the sham-treated mice as the main effect of PC lesion group was to impair d prime ($F_{(1,24)}$=6.1, p<0.05; Fig. 1C; Cohen's D=1.3). Despite main effects on d prime, PC lesions did not significantly lower hit rate (Fig. 1D), or elevate false alarm rates (Fig. 1E; Fs<1.8). Similarly, no PC lesion effect on responsivity index (Fig. 1F), premature responses (Fig. 1G), accuracy (Fig. 1H), or breakpoint was observed (Fig. 1I; Fs<1, ns), indicative of normal effort motivation of mice for food rewards (45). It is clear therefore, that mice with PC lesions exhibit distinct difficulties identifying the appropriate response-type when presented with target and non-target stimuli in the 5C-CPT.

DAT knockdown effect on 5-CSRTT and 5C-CPT

Interestingly, DAT KD mice exhibited better 5-CSRTT performance compared to WT mice as measured by reduced %omissions (target misses; $F_{(1,57)}$=7.0, p<0.01; Supplemental Figure 1B). No genotype effect was observed on any other measure, including accuracy, reaction-time, motoric impulsivity, or total trials (F<1, ns; Supplemental Figure 1C–E). When trained in the 5C-CPT, however, DAT KD mice exhibited poorer performance than WT mice as measured by reduced hit rate ($F_{(1,56)}$=3.2, p<0.05; Fig. 2B) as a result of increased %omissions ($F_{(1,56)}$=2.5, p<0.05; Fig. 2C) and elevated false alarms ($F_{(1,56)}$=16.4, p<0.001; Fig. 2E) that drove poorer d prime performance ($F_{(1,56)}$=14.5, p<0.001; Fig. 2D; Cohen's D=1.2). KD mice also exhibited increased premature responses (($F_{(1,56)}$=3.2, p<0.05; Fig. 2E), poorer accuracy ($F_{(1,56)}$=8.3, p<0.01; Fig. 2F) and slower reaction times ($F_{(1,56)}$=16.4, p<0.001; Fig. 2G) than WT mice in the 5C-CPT. Moreover, consistent with previous reports (46), these mice exhibited higher effortful motivation in a breakpoint study ($t_{(57)}$=−3.832, p<0.001; Supplementary Figure 2). Hence, reduced functioning of the DAT improved attention when only target stimuli appear (5-CSRTT), but impaired attention when both target and non-target stimuli were presented in the same task (5C-CPT).

5C-CPT deficits in BD mania

BD participants with mania exhibited poorer 5C-CPT performance as measured by lower responses to target stimuli (hit rate; ($F_{(1,22)}$=6.1, p<0.05; Fig. 3D), indicative of higher percent of omissions in manic BD participants ($F_{(1,22)}$=4.5, p<0.05), as well as a non-significant response disinhibition (elevated false alarms; ($F_{(1,22)}$=2.6, p<0.1; Fig. 3E). Combined, these impairments resulted in a primary attention/vigilance deficit in d prime ($F_{(1,22)}$=6.4, p<0.05; Fig. 3C; Cohen's D=0.7). A significant time-period X group interaction ($F_{(2,44)}$=6.2, p<0.05) revealed that although reaction time was equivalent in the first time

period, manic BD participants exhibited slower reaction times in time periods 2 and 3 compared to healthy participants ($p<0.05$). BD mania participants exhibited higher premature responses than HC ($F_{(1,22)}=14.8$, $p<0.001$), yet were as responsive to stimuli as HC as measured by the responsivity index (F<1.4, ns; Fig. 3G). Finally, BD mania participants did not exhibit differences in accuracy (F<2, ns; Fig. 3H).

5C-CPT performance in euthymic BD

On the 5C-CPT task without fMRI, BD euthymic participants performed somewhat equivalently to HC participants across several measures including d prime (Supplemental Figure 3A; Cohen's D=0.2), variability in reaction time, false alarm rate, and bias (F<1, ns). BD participants did tend to exhibit lower hit rates however [$F_{(1,93)}=3.4$, $p=0.06$; Supplemental Figure 3B), suggesting more lapses in attention in euthymic BD than healthy participants. Overall, participants made more %omissions over time ($F_{(2,186)}=7.9$, $p<0.001$), indicative of increased lapses in attention over the 3 blocks (1.1, 1.6, and 2.2% for blocks 1, 2, and 3 respectively), with higher levels in the BD group (($F_{(1,93)}=3.8$, $p=0.055$, 2.4, 2.6, and 3.5% for blocks 1, 2, and 3 respectively; Supplemental Figure 3C). Thus, sustained spatial attention was only modestly impaired among euthymic BD participants.

Brain response during 5C-CPT in euthymic BD

Consistent with results from behavioral testing without fMRI, performance on the 5C-CPT in the fMRI scanner in terms of hit rate, false alarms, d prime, and all other measures was equivalent in HC and euthymic BD groups (F<1, ns). During the period of attentional vigilance and target perception, just prior to initiation of the motor response, a widespread network of brain response was observed in both the BD and healthy groups. Activated regions included: premotor cortex; inferior parietal lobe; basal ganglia; and thalamus, replicating our previous findings (29). Response within these previously observed regions of interest was not statistically different between the two study groups (Supplemental Table 1), although right parietal response during target trials was non-significantly higher in the HC group than the BD group with a medium effect size (Cohen's D=0.57). During the period after the non-target signal, while participants were correctly refraining from responding, we found widespread response in areas such as the inferior frontal cortex, premotor cortex, presupplementary motor area, and inferior parietal lobe, consistent with our previous work (29). Response within these *a priori* regions of interest did not differ significantly between the euthymic BD and comparison groups (Supplemental Table 1), although response in the left precentral gyrus cluster during non-target trials was non-significantly higher in the HC group (Cohen's D=0.59).

Since there was considerable variability in brain response among the BD group, we tested whether euthymic BD participants who reported higher impulsivity during positive mood states (perhaps indicative of a tendency to exhibit more severe symptoms during manic episodes) might represent a subgroup with more impaired attentional brain response. Indeed, those with greater impulsivity during positive mood showed a different pattern of brain activation in response to target and non-target trials in many of the regions of interest compared to controls (Figure 4). Of note, those with higher self-rated impulsivity had lower response to targets in the right PC (r(15)=0.55, p=0.02) and lower response to non-targets in

the right (r(15) = 0.58, p=0.01) and left (r(15)=0.48, p=0.05) PC. Response to non-targets within prefrontal regions of interest was also lower among those with higher self-rated impulsivity (Supplemental Table 2). Although statistical corrections were used to account for demographic differences between HC and BD in the imaging study, it is possible that a better-matched HC sample would have revealed more brain response deficits in the euthymic BD patients as a group.

DISCUSSION

The parietal cortex (PC) is required for attentional tasks when both target and non-targets, as supported by our work in the 5C-CPT wherein bilateral PC lesions impair mouse performance while human fMRI studies reveal PC activity during performance. Importantly, out of the scanner, people with BD euthymia exhibited deficient 5C-CPT performance, while their in-scanner fMRI performance revealed PC brain responses related to impulsivity. A more pronounced 5C-CPT deficit was observed in BD mania patients, consistent with our observations in mice with reduced DAT levels. Hence, there may be links between PC function and DAT levels in relation to attentional deficits in BD.

Interestingly, bilateral PC lesions did not induce specific deficits in target or non-target trials but deficient overall performance as measured by d prime, as commonly measured in human studies (47) (29). Furthermore, the data confirm that the PC is not required in mice for simple accuracy discrimination (responding to lit vs. unlit holes) during target trials as seen with rats in the 5-CSRTT (48). It was also interesting to note that the DAT KD mice exhibited better performance than their WT littermates (lower %omissions) in the 5-CSRTT, which requires responses only to target trials. In contrast, when required to also inhibit from responding as in the 5C-CPT, they exhibited poorer performance (higher %omissions and false alarms). These findings add support to the premise that in order to assay attention across species, consistent with human CPT studies, both target and non-target trials must be presented (6, 38).

In previous work, it was determined that mice with 0% expression of the DAT (knockout mice), could not be trained in the 5-CSRTT (49). Hence, while 0% is severely detrimental to learning such a task, 10% expression, as in the present study, can be beneficial to learning and performance of this standard target-only task. In contrast, 50% expression as seen in heterozygous mice, resulted in reduced accurate target responding in the 5-CSRTT in young and adult male mice, although overall %correct remained unaffected (49, 50). The level of DAT expression could therefore negatively impact this target-only task, and alters performance when non-target stimuli are included, such as in the 5C-CPT. A systematic approach toward understanding attentional performance of mice across DAT expression will be useful in future studies. In contrast with mice after PC lesions, DAT KD mice exhibited higher motoric impulsivity, which could be driven by the striatal hyperdopaminergia of these mice (35), as it has been linked to motoric impulsivity/poor timing in rodents (51). DAT KD mice are also reliably hyperactive (52), and their hyperactive profile may have contributed to improved performance in tasks that required target responding only (5-CSRTT). This hyperactivity was unlikely to drive deficits in DAT KD performance in the 5C-CPT however, given that although they exhibited higher levels of false alarms (non-target responses), they

exhibited fewer hits (target responses). Importantly therefore, their bias of responding was unchanged, indicative of normal response levels compared to WT mice. Hence, both PC function and DAT levels are important in mouse attentional performance

BD mania patients exhibited a similar profile of poor attention in the 5C-CPT as DAT KD mice, reduced target responding and elevated false alarms, in addition to higher premature responses when compared with HC participants. The BD euthymia studies demonstrate that such inattention is a trait deficit in BD - seen even in a younger and more educated group than the healthy comparison participants. The fMRI study also demonstrated the importance of the PC during task performance in addition to highlighting altered PC brain response within euthymic BD whom exhibited mood-related impulsivity. Hence, reduced PC DAT could explain the poor distinction of responding to target vs. non-target in these mice, while reduced striatal DAT could drive deficits in additional aspects of behavior.

The link between PC and DAT function is consistent with evidence that DAT is expressed in both mouse (53–55) and primate PC (56). Hence, PC DAT may contribute to the poor attention of BD mania patients measured using various CPTs. Directional DAT effects on PC function can be seen whereby chronic amphetamine treatment to mice (a norepinephrine transporter and DAT inhibitor) altered PC gene expression (57). More selective DAT inhibition can also affect PC expression such as *Homer 1a* expression (58), consistent with the observation that reduced DAT expression downregulates *Homer 1a* expression also in the prefrontal cortex (49). Interestingly, frontal and PC injury reduces DAT expression (59, 60). The pattern of 5C-CPT deficits seen in the PC-lesioned and DAT KD mice, characterized by poorer target responding and elevated non-target responding, is consistent with similar deficits in BD mania patients in the literature (61, 62) and in this spatial visual array 5C-CPT (38).

Cognitive abilities, including attention, are compromised in BD participants even in the absence of mood symptoms (63, 64). For example, a recent study (65) used the AX version of the CPT and found that euthymic bipolar participants behaved normally in the early blocks of the task (trials 1–50), but by the fourth block (trials 150–200) showed greater misses and false alarms, resulting in a lower d prime. Thus, the PC-DAT neural mechanism that we propose for BD mania may also play a role in attentional deficits observed in the absence of mood symptoms. Modest cognitive deficits were observed in BD euthymic participants (increased omissions), with broadly similar brain responses compared with healthy participants. Importantly, however, reduced PC and frontal activation during both trial types was related to greater self-rated impulsivity in BD, suggesting that even during euthymia, those with trait behavioral dysregulation in response to positive mood have altered prefrontal and PC responses. These data indicate that a fronto-parietal network is a key system mediating cognitive control behavior in BD – consistent with other CPTs (66) – likely interacting with reduced dopamine clearance mechanisms within this system.

These data provide further support for the link between the DAT, PC, and altered cognitive processing in mental illness (10). This cross-species work also highlights the importance of reduced DAT functioning negatively impacting attention, in accordance with evidence for the 10 random repeat allele variant of DAT being associated with response disinhibition in

ADHD and linked to altered PC activation (67). ADHD patients with the 10 random repeat alleles performed poorer on the CPT and had lower EEG-based parietal beta power while performing a CPT than those with the 9 repeat alleles (68). These data indicate that the DAT polymorphism may affect PC neural activity. Additionally, increasing working memory/attentional load also separates out DAT allelic variants for higher fronto-striatal-parietal activation neural network responses in ADHD children (69). Collectively, these data indicate that reduced PC DAT functioning drives impaired attentional performance of participants with BD mania, and also possibly children with ADHD. Given the importance of parietal function across CPTs (70), it is also possible that altered PC function negatively impacts other disorders such as schizophrenia or additional phases of BD such as depression. Future studies should address this limitation and include other populations and phases of BD illness. The present findings that BD participants with acute mania (within 72 hours of hospitalization) demonstrated significant 5C-CPT deficits support these findings and add further evidence to the clinical sensitivity of the 5C-CPT (38). Only subtle attentional deficits were observed in BD euthymic patients, however, whereas more difficult tasks, e.g., degraded stimuli or distracters that lowered PC activity, were required to observe robust performance deficits in euthymic BD patients (71, 72). The use of such additional cognitively demanding aspects to CPTs, e.g., degraded stimuli or working memory, could reduce the selectivity of performance to the attentional domain (73, 74) however. For example, the AX-CPT was promoted by CNTRICS as a test of working memory (goal maintenance) as opposed to attention (75). Importantly however, among our euthymic BD participants, the degree to which they endorsed impulsive behavior during positive mood states related strongly to the degree of PC activation during both target and non-target trials. Therefore, while the euthymic group as a whole may not show the same extreme deficits of PC function during attention seen during mania, individuals who tend to act out during episodes of elevated mood show reduced PC response even when their mood is normal.

These data also reveal a separation of PC/BD state performance. Despite modest deficits, neither mice with PC lesions nor people with BD euthymia exhibited elevated premature responses. In contrast however, both DAT KD mice and BD mania patients exhibited elevated premature responses in the 5C-CPT. Hence, unlike chronically ill patients with schizophrenia (38, 76, 77), BD mania patients exhibit elevated premature responses. This measure has been associated with motoric/waiting impulsivity and/or temporal processing (51, 78). The lack of effect in PC-lesioned mice or BD euthymia patients indicates that a separate region subserves this behavior, likely overlapping brain regions high in DAT density such as striatal regions. Regionally targeted DAT reduction, and/or restoration of knockdown mice (79), during 5C-CPT performance would be required, however, to test such a hypothesis.

Several limitations exist within these studies. One is that while the majority of people with BD tested were female, the mice tested were only male. While both male and female DAT KD mice exhibit hyperactivity and altered behaviors relative to their WT littermates (18, 20, 52, 80), the testing of only males here limits the generalizability of our mouse findings of attention to the general population. All of our mouse cognitive testing now includes females to address this potential concern. It is recognized that the DAT KD mice tested here exhibit reduced DAT throughout the brain throughout their lives, not just in the PC or at the time of

testing. Although acute DAT inhibition with GBR12909 recreates many of the BD-relevant behaviors of DAT KD mice (19, 20, 81), future studies will determine the localized effect of PC DAT KD as these techniques become available. For example, comparing PC vs. striatal DAT KD could be key in future studies delineating circuitry underlying these behaviors and those contributing to deficits in patients. Finally, we recognize that although varied medications may have impacted these results, the consistency between those BD sufferers on long-term medication (euthymia) and recent (mania), suggests that it is unlikely that the observed differences were a result of medication.

Collectively, our data support the hypothesis that reduced DAT function underlies the impaired attentional functioning of patients with BD mania, possibly linked to changes in the PC that occur during BD euthymia. These data have clinical implications wherein novel treatment strategies for BD may be effective if they target the DAT to improve attention which may have the downstream beneficial impact of reducing impulsivity and stabilizing mood. Availability of this cross-species 5C-CPT enables future studies investigating more regional and temporal selectivity of reduced DAT function on attentional performance in mice, the effect of BD medication on performance, and the contribution of PC dysfunction in other disorders. Furthermore, fMRI attentional testing should be attempted in BD patients, and/or medication-free euthymic BD participants across states (mania, euthymia, and depression) in a more challenging 5C-CPT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. Maureen Martin and Ms. Mahalah Buell for their invaluable support during these studies. These studies were made possible by funding from NIMH grant R01-MH104344, R01-DA043535, R01-MH071916, R21-MH085221, UL1RR031980, as well as by the Veteran’s Administration VISN 22 Mental Illness Research, Education, and Clinical Center.

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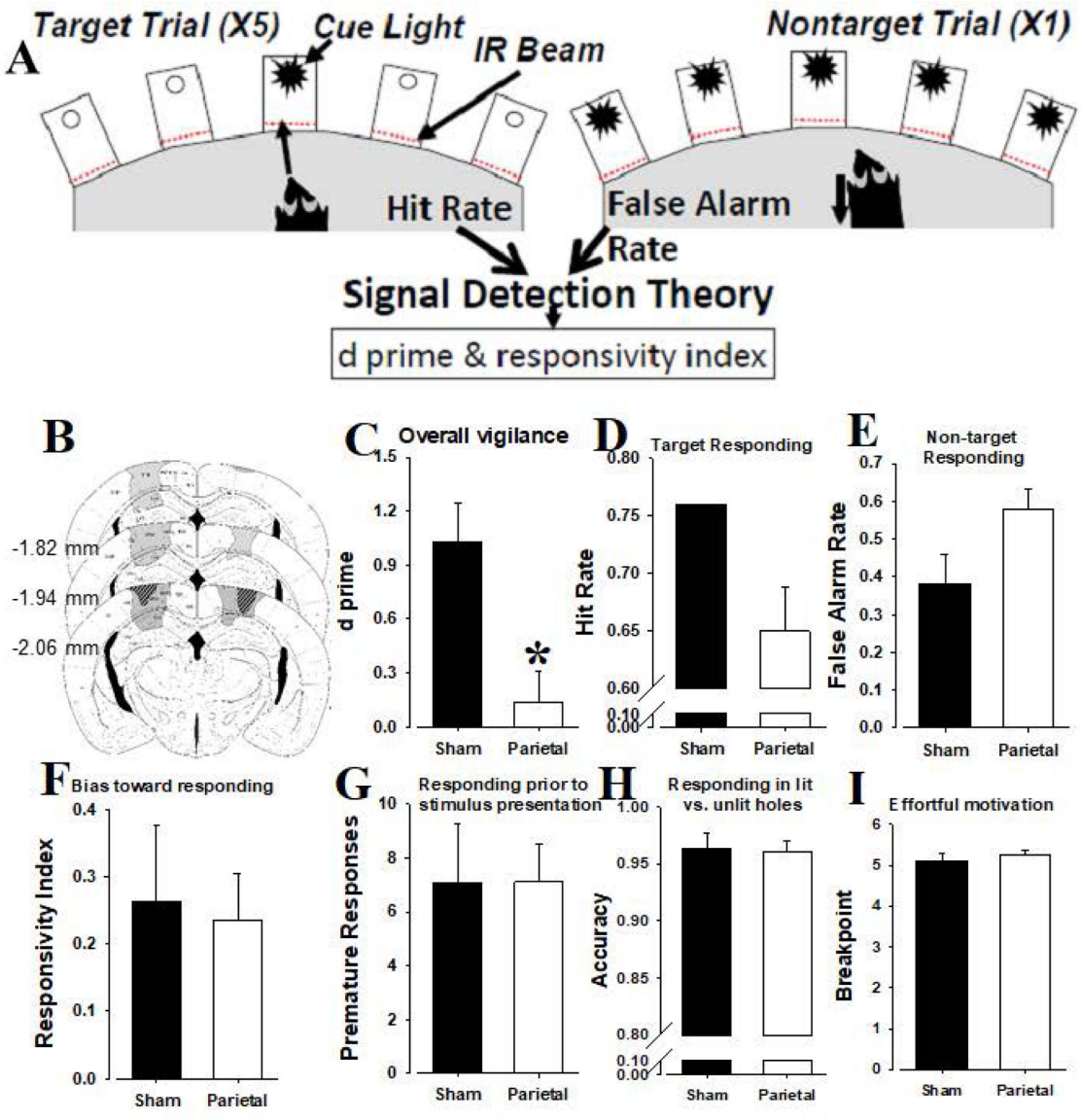

Figure 1. Parietal lesions impair 5C-CPT performance in mice.

The 5C-CPT was designed consistent with human CPTs (**A**) wherein target trials (singly lit apertures) are presented interspersed with less frequent non-target trials (all lit apertures). Responses at each aperture are recorded by breaking the infra-red beams (red dashed line). C57BL/6J mice (n=24) received (**B**) bilateral parietal cortex lesions (Parietal) with ibotenic acid or sham lesions (aCSF). Parietal lesions impaired overall performance of the task (**C**) as measured by d prime, which is the combined performance of target responding and inhibition of the non-target responding. Parietal lesions did not significantly reduce target responding (hit rate; **D**) over time, or elevate non-target responding (response inhibition; **E**), nor alter bias level of responding (**F**) as measured by responsivity index. Parietal cortex lesions also did not alter responding before stimuli appeared (premature responses; **G**) a measure of motoric impulsivity/temporal performance, nor the ability of mice to respond in lit vs. unlit holes (accuracy; **H**) consistent with observations in the 5-choice serial reaction-

time task. Finally, parietal cortex lesions did not affect effortful motivation as measured by breakpoint (**I**).

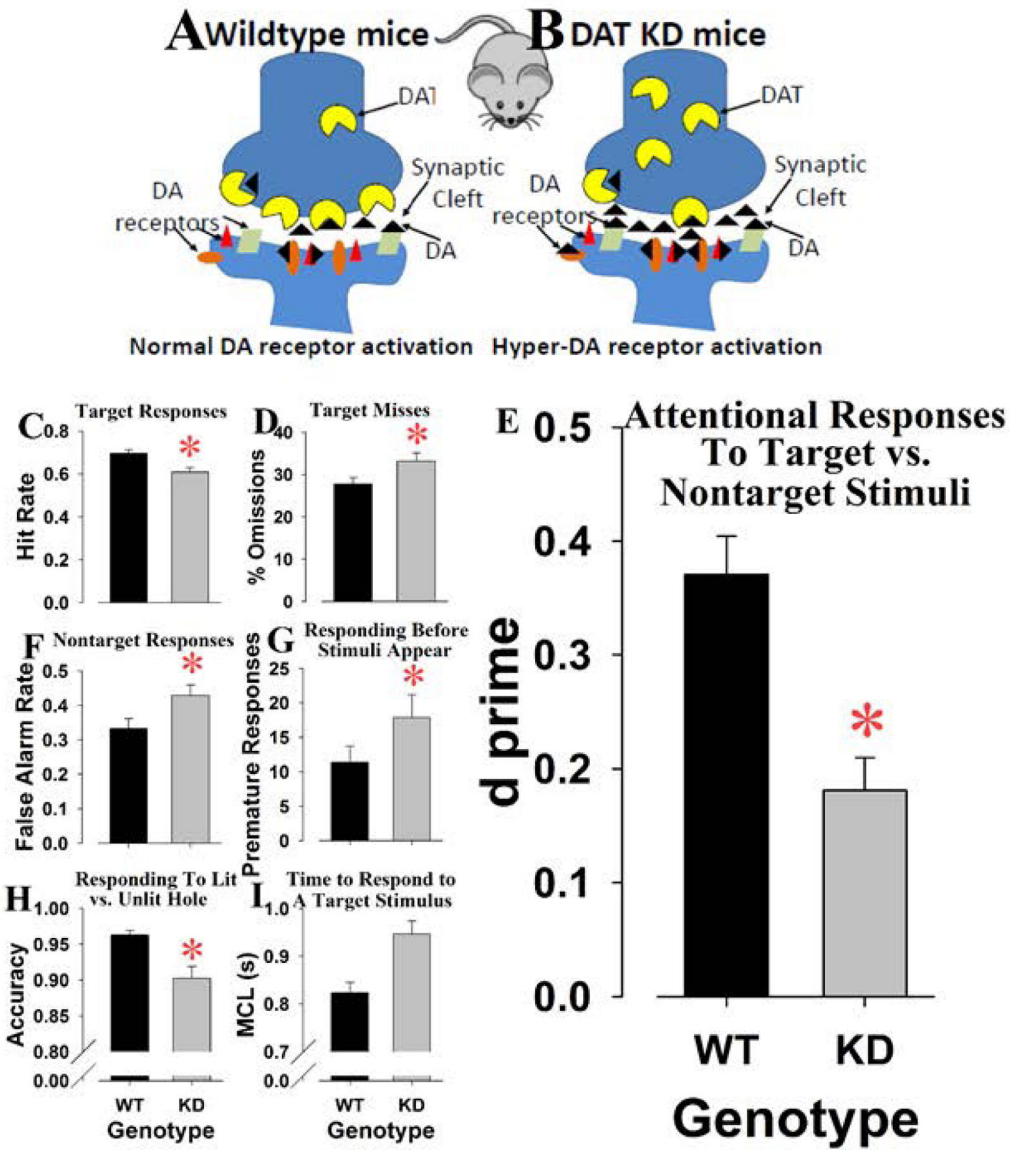

Figure 2. Impaired 5C-CPT performance of DAT KD mice.

Dopamine transporters (DAT) are integral to maintaining dopamine homeostasis in the synaptic cleft. DAT is the primary source of dopamine reuptake from the synaptic cleft, limiting dopamine receptor activation (**A**). DAT knockdown (KD) mice exhibit 10% of DAT vs. their wildtype (WT) littermates, resulting in higher levels of dopamine in the synaptic cleft (**B**). When trained in the 5-choice continuous performance test (5C-CPT), DAT KD mice (n=31) exhibit significantly poorer performance vs. WT (n=28) mice as measured by target stimuli detection as measured by hit rate (**C**), similarly to % omissions (**D**). This poor target detection largely drove the impaired overall vigilance scores of DAT KD mice as measured by d prime (**E**). DAT KD mice also exhibited response disinhibition deficits, as measured by a higher false alarm rate (**F**). These mice also responded more often when stimuli were not present, indicative of poorer response control (**G**). DAT KD mice were also less accurate during the 5C-CPT, responding to unlit holes during target trial presentation

more than WT mice (**H**). Finally, despite slower choice latencies, these mice exhibited a non-significant slowing of responding (**I**). Data presented as mean + S.E.M., * denotes $p<0.05$ compared with WT littermates.

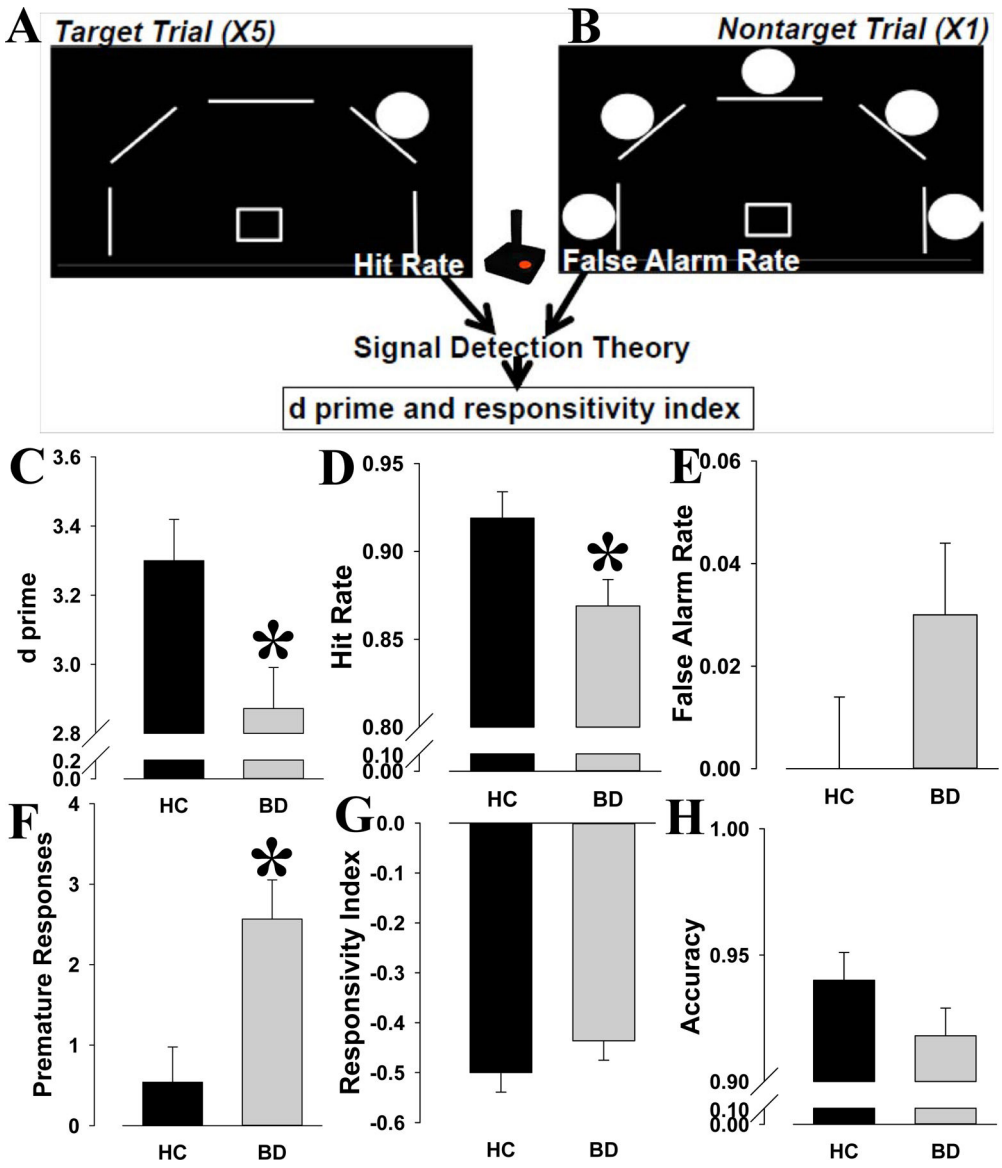

Figure 3. Impaired 5C-CPT performance of BD mania patients.

The ability of acutely manic patients with bipolar disorder (BD, n=13) to perform the 5-choice continuous performance test (5C-CPT) was examined and compared with healthy comparison subjects (n=9). The human 5C-CPT required participants to use a joystick to respond to target stimuli when a single circle appears (**A**), but inhibit from responding to non-target stimuli, when 5 circles appear (**B**). BD mania patients exhibited significantly worse overall vigilance than HC as measured by d prime (**C**). This impairment was driven by increased misses to target stimuli as measured by hit rate (**D**), but also a non-significant increase in response disinhibition, responding to non-target stimuli (**E**). Increased premature responses were observed in mania patients vs. HC participants (**F**). Hence, the bias of responding in patients did not differ from HC participants, as measured by responsivity index (**G**). Mania patients did exhibit fewer accurate responses in the direction of target

stimulus location vs. other locations (**H**). Data presented as mean + S.E.M., * denotes $p<0.05$ compared to HC participants.

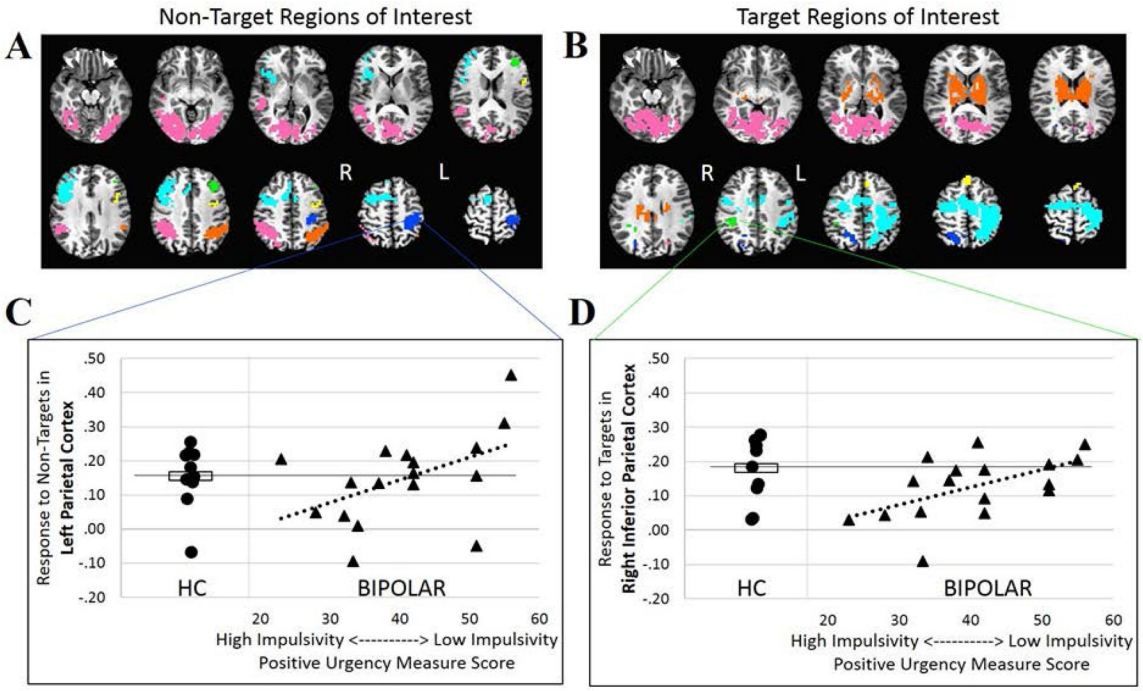

Figure 4. Higher impulsivity linked to lower parietal cortex (PC) brain response during target and non-target trials of the human 5C-CPT in euthymic BD.

In regions of interest in which significant brain response was observed in an independent sample of healthy individuals (n=10; [21]; each ROI colored differently to show the distinct regions) during correct inhibition of response to non-target trials **(A)** and just prior to motor response during target trials **(B)**, brain response of 10 new healthy individuals and 10 euthymic bipolar disorder patients was measured during non-target and target trials, respectively. There were no significant differences in brain response (as measured by mean fit coefficient of the contrast of interest) between the two groups in any region, but within many regions, including the left PC non-target region of interest **(C)** and the right inferior PC target region of interest **(D)**, those BD patients (triangles) who rated themselves as more impulsive during positive mood states (low scores on the Positive Urgency Measure) had lower brain response (dotted line is best fitting line; both correlations are significant: non-target left parietal $r(15) = 0.48$, $p = 0.05$, target right inferior parietal $r(15) = 0.55$, $p = 0.02$)). Those with the greatest impulsivity had brain response lower than the healthy comparison group (circles) mean (rectangle and horizontal line).

Table 1:

Demographics of acutely ill patients with bipolar disorder (BD) mania vs. healthy comparison (HC) participant.

	Group Means (± SD, min-max)		
Demographics	**HC (n=13)**	**BD (n=9)**	***p-value***
Mean Age (yrs.)	33.4 (±13.7, 20–56)	32.6 (±14.7, 19–58)	*ns*
Education	15.0 (±1.55, 14–17)	14.8 (±1.9, 13–19)	*ns*
Sex (% male)	33.3%	23.1%	*ns*
YMRS		19.9 (±8.5, 9–36)	

Table 2:

Demographics of patients with euthymic bipolar disorder (BD) vs. healthy comparison (HC) participants tested in the behavioral paradigm.

	Group Means (± SD, min-max)		
Demographics	**HC (n=55)**	**BD (n=40)**	***p-value***
Mean Age (yrs.)	47.9 (±14.3, 30–68)	46.4 (±11.1, 30–67)	*ns*
Education	14.9 (±2.3, 11–20)	15.5 (±2.1, 12–20)	*ns*
Sex (% male)	57%	70%	*ns*
YMRS		0.9667 (±0.2311, 0–4)	

Table 3:

Demographics of patients with euthymic bipolar disorder (BD) vs. healthy comparison (HC) participants tested with fMRI.

	Group Means (± SD, min-max)		
Demographics	**HC (n=10)**	**BD (n=27)**	***p-value***
Mean Age (yrs.)	54.3 (±12.1, 37–65)	44.8 (±11.4, 30–67)	*0.05*
Education	13.9 (±1.7, 12–16)	16.0 (±2.2, 12–20)	*0.005*
Sex (% male)	60%	48%	*ns*