Neuropsychopharmacology (2017) 42, 1338–1348

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Neurophysiological Characterization of Attentional Performance Dysfunction in Schizophrenia Patients in a Reverse-Translated Task

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Attentional dysfunction in schizophrenia (SZ) contributes to the functional deficits ubiquitous to the disorder. Identifying the neural substrates of translational measures of attentional dysfunction would prove invaluable for developing therapeutics. Attentional performance is typically assessed via continuous performance tasks (CPTs), though many place additional cognitive demands with little cross-species test-relevance. Herein, event-related potentials (ERPs) were used to investigate the neurophysiological correlates of attention and response inhibition of SZ and healthy participants, whereas they performed the cross-species-translated five-choice CPT (5C-CPT). Chronically ill, medicated SZ patients and matched controls ($n = 25$ SZ and 26 controls) were tested in the 5C-CPT, in conjunction with ERP and source localization assessments. The ERPs generated in response to correctly identified target and non-target trials revealed three peaks for analysis, corresponding to sensory registration (P_1), response selection (N_2), and response action (P_3). Behavioral responses revealed that SZ patients exhibited impaired attention driven by impaired and slower target detection, and poorer cognitive control. ERPs revealed decreased N_2 amplitudes reflecting poorer response selection for both target and non-target trials, plus reduced non-target P_3s in SZ patients, the latter accounting for 37% of variance in negative symptoms. Source analyses revealed that the brain regions of significant differences localized to the left dorsolateral prefrontal cortex during response selection and the posterior cingulate cortex for cognitive processes. SZ patients exhibited impaired attention and cognitive control, characterized by less robust frontal and parietal ERP distributions across the response selection and cognitive response time windows, providing neurophysiological characterization of attentional dysfunction in SZ using the reverse-translated 5C-CPT.
Neuropsychopharmacology (2017) **42,** 1338–1348; doi:10.1038/npp.2016.268; published online 8 February 2017

INTRODUCTION

Patients with schizophrenia (SZ) exhibit poor cognitive performances across numerous domains, which correlate with their ability to live independently (Green, 1996; Green *et al*, 2008). Considering current treatments predominantly target only positive symptoms of the illness, with limited-to-no efficacy for treating these disabling cognitive deficits (Keefe *et al*, 2007; Parks *et al*, 2008), research has been galvanized toward identifying procognitive treatments for SZ patients. To date, vast numbers of clinical trials for psychiatric patients have failed at the cost of time, effort, billions of dollars, and the hope of the patients being tested. Many of these trials were based on positive preclinical data that failed to demonstrate efficacy in human trials. Failed human trials are often attributed to the lack of consistency in quantifying the same neural processes across species and the use of 'fast and dirty' behavioral techniques that have little-to-no relevance to human testing (Sarter, 2004). To that end, the National Institutes of Mental Health (NIMH) formed the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) to identify behavioral paradigms that could be tested across species with translational validity (Carter and Barch, 2007; Dudchenko *et al*, 2013; Gilmour *et al*, 2013; Lustig *et al*, 2013) and promote the use of biomarkers of neural systems engaged during performance of these cross-species translational paradigms (Barch *et al*, 2012; Carter and Barch, 2012; Luck *et al*, 2011). An important initial step in such national initiatives is to establish what, if any, cognitive deficits and

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Received 7 July 2016; revised 25 October 2016; accepted 4 November 2016; accepted article preview online 5 December 2016

their associated biomarkers of neural system measures are apparent in putative cross-species translational paradigms.

The five-choice continuous performance test (5C-CPT), originally developed for testing in mice (Young *et al*, 2009), was highlighted by the CNTRICS initiative as a promising cross-species paradigm for assessing the control of attention (Lustig *et al*, 2013). Consistent with other human CPTs, the 5C-CPT presents and requires responses to targets and inhibition of responses to non-target trials. Importantly, with more target than non-target trials, the 5C-CPT measures the control of attention, because it theoretically requires subjects to inhibit a prepotent response (Ford *et al*, 2004; Lustig *et al*, 2013), although to our knowledge, this has not yet been empirically demonstrated.

In terms of evidence for cross-species translational validity, we have observed the following in rodents and in humans: (a) 36 h sleep deprivation-induced deficits (van Enkhuizen *et al*, 2014); (b) amphetamine-induced improvement (MacQueen et al, in preparation); (c) parietal requirement for performance from human functional magnetic resonance imaging (fMRI) and rodent lesion studies (McKenna *et al*, 2013b); and (d) vigilance decrement observations across time (Young *et al*, 2013a; Young *et al*, 2009). Hence, consistent with a signal detection task, manipulation-induced changes in performance can be consistent across species (Bushnell *et al*, 2003). Importantly, the human 5C-CPT is also clinically sensitive, as patients with SZ exhibit deficient performance (Young *et al*, 2013a), consistent with other CPTs (Cornblatt and Keilp, 1994; Nuechterlein, 1991). Characterization of neural processing measures underlying normal and impaired behavioral performance of SZ patients in this cross-species task could therefore accelerate the development of procognitive therapeutics that target attentional systems, as drug effects observed on this task in animals may be more likely to span the translational bridge to human trials. fMRI studies can be conducted in the 5C-CPT (McKenna *et al*, 2013b), but such studies would prove difficult to conduct in rodents. In contrast, electroencephalographic (EEG) studies are possible in both humans (Bickel *et al*, 2012; Kleinlogel *et al*, 2007) and rodents (Brigman *et al*, 2013; Nagy *et al*, 2015), although knowledge of EEG response dynamics in patients with SZ is required before adaptation for rodent models (Featherstone *et al*, 2015; Gandal *et al*, 2010).

Although numerous studies have examined biomarker/attentional performance in impaired neuropsychiatric patients via the examination of event-related potential (ERP) responses to infrequent target oddball stimuli (eg, N_{200} or N_2 and P_{300} or P_3 (Turetsky *et al*, 2015)), such oddball tasks are rarely, if ever, used in clinical neuropsychological assessments of patient populations. Conversely, computerized CPTs are frequently used in clinical evaluations, but relatively few studies have assessed the neural substrates of cognitive control using translatable CPTs, given the relative dearth of available tasks with cross-species validity. Previous studies found decreased ERP amplitudes in patients with SZ and their first-degree relatives, in particular late amplitudes of posterior parietal regions (P_3), and augmented early amplitudes over frontal regions (anterior N_{100} or N_1) (Sponheim *et al*, 2006), with reduced P_3 amplitudes in patients with SZ (Clementz *et al*, 2008; Knott *et al*, 1999) and in children at risk (Friedman *et al*, 1986). Interestingly, when P_3 amplitudes over midline scalp sensors were examined in response to target and non-target trials, the lack of amplitude differences by stimulus type in patients correctly classified all patients and controls (Knott *et al*, 1999). Although target and non-target ERP scalp topographies are fairly consistent across studies, testing modality (auditory *vs* visual) can alter ERP amplitude and latency differences relevant to the interpretations of sensory and attentional functioning seen in SZ (Tekok-Kilic *et al*, 2001; Morales-Muñoz *et al*, 2016). Source localization analyses of high-density EEG recordings during CPTs (Doehnert *et al*, 2010) may help resolve contradictory findings in earlier studies. This study aimed to characterize and determine the electrophysiological correlates of 5C-CPT performance in patients with SZ and healthy controls (HCs). We hypothesized that patients with SZ would exhibit the following: (1) impaired 5C-CPT performance; (2) altered difference wave ERP amplitudes (between target and non-target trials); and (3) altered source localizations relative to HC participants.

MATERIALS AND METHODS

Participants

SZ outpatients ($n=25$), and gender and age-matched HCs ($n=26$) participated in the current study (Table 1). Written informed consent was obtained in accordance with University of California San Diego institutional review board-approved procedures. Participants were assessed diagnostically using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (First *et al*, 1995), the Scale for the Assessment of Negative

Table 1 Demographic Means and SD by Group for Age, Education Level, and Smoking Status (Smoker *vs* Non-Smoker) of Healthy Comparison Subjects (HC) and Patients with SZ

Demographics	Group means (±SD, min–max)		*p*-value
	HC ($n=26$)	SZ ($n=25$)	
Mean age (years)	37.8 (±10.9, 21–55)	41.4 (±11.7, 23–60)	NS
Education	14.6 (±2.2, 11–19)	13.4 (±2.3, 7–18)	NS
Sex (% male)	62%	80%	NS
Smoking	31%	36%	NS
Right handedness	92%	80%	NS
Age of onset (years)		21 (±6.4, 10–40)	
Illness duration (years)		22 (±10.5, 1–37)	
SAPS total score		6.5 (±4.0, 0–13)	
SANS total score		16.7 (±4.4, 6–24)	
GAF		42.2 (±6.9, 36–73)	
	Patients receiving medication type, no.		
	Typical (exclusively)	5	
	Atypical (exclusively)	18	
	Typical+atypical	3	

Abbreviations: HC, healthy control; NS, not significant; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SZ, schizophrenia.
No significant differences for any demographics were observed.

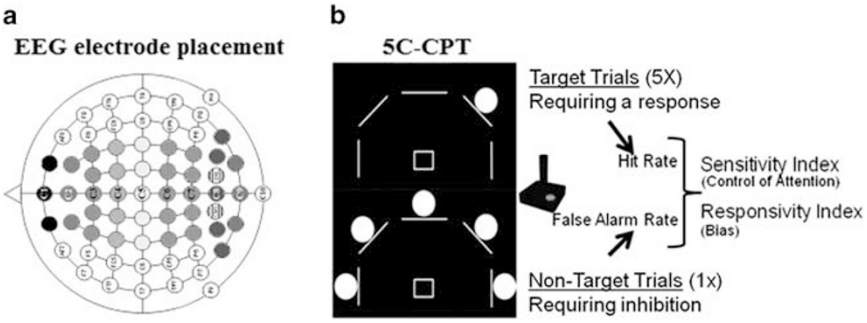

Figure 1 Task schematics. Schematic of centroid mapping indicated by number, calculated according to weighted averages of neighboring channels as indicated by color (a). Five-choice continuous performance task (5C-CPT) schematic (b), where target trials are presented by a single circle (top), requiring a response from the joystick in that direction (up and left in the example provided), whereas non-target trials are presented by five circles (below), requiring the inhibition of responding. Target trials contribute to the hit rate (HR) measurement, whereas non-target trials contribute to the false alarm rate (FAR) measurement (response inhibition). These measures are combined to produce the primary outcome measure for control of attention, the SI, whereas responsivity index measures bias of responding.

Symptoms (SANS; Andreasen, 1983), the Scale for the Assessment of Positive Symptoms (Andreasen, 1984), and the modified Global Assessment of Functioning Scale (Hall, 1995). SZ patients did not have an Axis I diagnosis other than SZ and HCs did not have any Axis I diagnosis. Exclusion criteria included drug abuse or dependence within the last 2 months, neurologic insult such as significant head trauma and/or loss of consciousness.

Task: 5C-CPT

Consistent with previous reports (Young *et al*, 2013a), the participants were given a brief practice on the task (see Supplementary Information). They were instructed to move the joystick in the direction a circle (target stimuli) appears, but inhibit from responding if five circles appeared simultaneously (non-target stimuli; Figure 1b). After a joystick response, the line under the selected stimulus flashed to indicate which target was selected, otherwise no other feedback was provided irrespective of accuracy. Stimuli were presented for 100 ms in a random order to reduce temporal predictability (Cope *et al*, 2016), with a 1 s response window available and a variable inter-trial intervals (0.5, 1, or 1.5 s). All participants understood the task and correctly performed the practice block before initiating the session. The full task consisted of 648 trials, 540 target stimuli, and 108 non-target stimuli, presented pseudorandomly so that no more than 3 presentations of a specific stimulus appeared consecutively.

Responses were recorded and include hits (correctly responding to a target stimulus) and misses (omissions, not responding to a target stimulus), incorrects (responding to locations other than the target), as well as false alarms (FAs; responding to non-target stimuli) and correct rejections (withholding from responding to non-target stimuli). Composite metrics of task performance were used in the analysis of performance, including hit rate (HR), and FA rate (FAR) as indicated in our previous work (Young *et al*, 2013a). The sensitivity and responsivity indices (measures of vigilance and bias respectively) were also calculated using signal detection theory (Green and Swets, 1966; McNicol, 1972), the former measures appropriate responding (Frey and Colliver, 1973) and the latter provides a measure of the 'tendency to respond' (bias).

Electrophysiological Recording and Data Processing

Continuous electrophysiological (EEG) data were recorded using a BioSemi Active Two system. During data acquisition the electrode offsets were kept below 25 mV and all channels were referenced to the system's internal loop (CMS/DRL electrodes). Data were recorded in DC mode from 64 scalp leads, four electrooculogram leads recorded at the superior and inferior orbit of the left eye and outer canthi of each eye, one nose, and two mastoid electrodes for offline re-referencing. All data were collected using a 1048 Hz sampling rate using a first-order anti-aliasing filter and all preprocessing occurred offline using Brain Vision Analyzer 2.0 (Brain Products GmbH). Bad channels were interpolated using a spherical spline interpolation and re-referenced to the average reference. Data were digitally band pass filtered between 1 and 70 Hz (24 db/oct) using a Butterworth zero phase-shift filter with 48 db/octave rolloff and eye movement artifacts were corrected using our established procedures. Epochs were generated from − 100 to 700 ms post stimulus onset for correct trials. Only correct trials were used for ERP analysis due to the low number of task related errors. Epochs with additional EEG artifacts (adjacent sample amplitudes and/or max voltage changes exceeding $\pm 70\,\mu V/ms$) were rejected and all remaining epochs were baseline corrected from − 100 to 0 ms. Separate ERP waveforms were generated for target and non-target trials.

Difference waves for each subject were generated by subtracting the target wave from the non-target wave. As in previous CPT ERP studies, centroids were calculated using the mean amplitude of channels centered on a midline channel and extending bi-laterally forming a strip of electrodes (eg, Centroid 3 = Mean of F_z, F_1, F_2, F_3, F_4; Fallgatter *et al*, 2002 and Figure 1a). Based on this methodology, no-go anteriorization (NGA) values were generated and compared. Hence in addition, *a priori* ERP analyses focused on results from centroid peaks (Knott *et al*, 1999). Group-level grand average waveforms indicated three distinct time windows during which subject-level ERP peaks (point with greatest absolute maxima within a time window) were selected for statistical analysis, thought to represent early sensory components ((100–150 ms; P_{100} or P_1; Herrmann and Knight, 2001), a middle latency transitional wave corresponding to response selection (150–250 ms; N_{200} or N_2), and later temporal

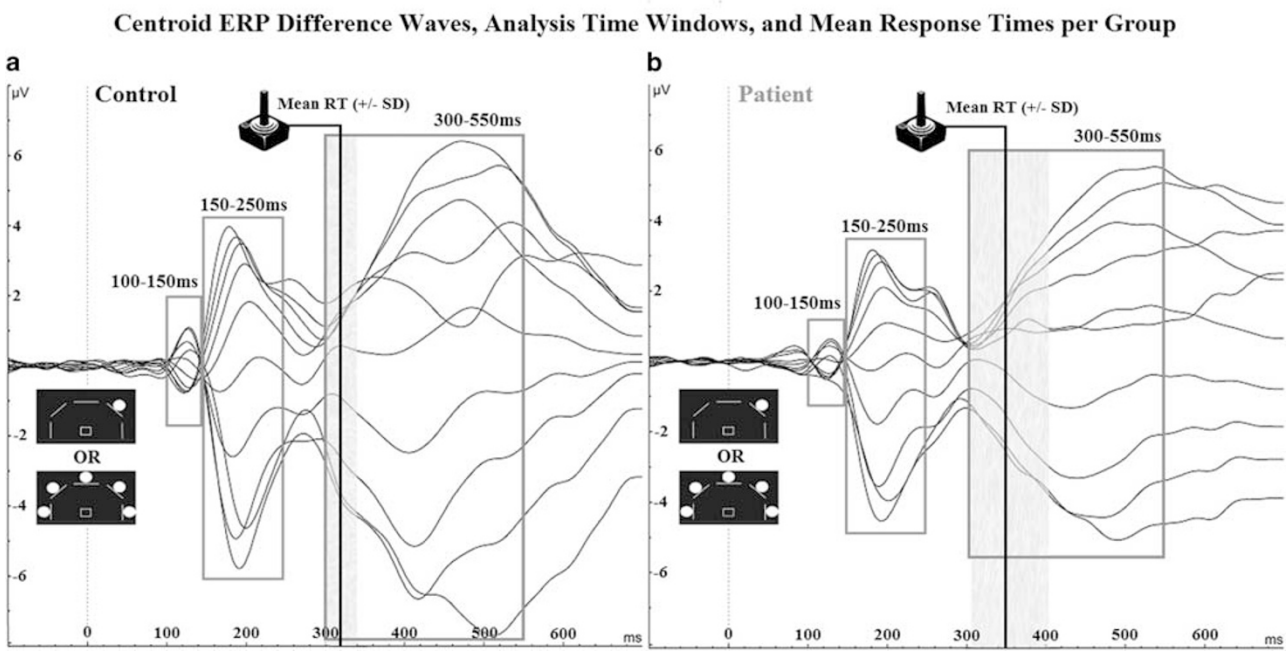

Figure 2 Electroencephalographic (EEG) butterfly plots. Butterfly plots of centroid difference waveforms and time windows for analysis (100–150, 150–250, and 300–550 ms) for healthy comparison subjects (control; a) and schizophrenia patients (b). Vertical black lines indicate mean reaction time for each group with shaded areas indicating standard deviation.

window that corresponded to response action and visual feedback of choice (300–550 ms; P_{300} or P_3; Figure 2).

Source Analysis

Source analysis of the ERP peaks was done in the Brainstorm environment using the Standardized low-resolution brain electromagnetic tomography algorithm (Pascual-Marqui, 2002; Tadel *et al*, 2011). A three-sphere head model was used and the source space was constrained to the cortex of a template brain with 3006 voxels (Berg and Scherg, 1994). The source image data was calculated at every time point for each subject. To test for group differences, the source image data for each subject was averaged across a 20 ms window centered over each of the three peaks for the group averaged ERP. Comparisons were done using cluster-based permutation statistics (1000 Monte Carlo simulations; (Maris and Oostenveld, 2007)). Separate source analyses were done for the target and non-target ERP waveforms. To compare with the centroid result, the same statistical comparisons were also done for the wider windows chosen for the ERPs.

Statistical Analyses

One-way multivariate analyses of variance (MANOVAs) and χ^2-tests (where appropriate) were used to compare group differences in demographics, behavioral task performance, and ERP amplitudes across trial types, time windows, and centroids. Spearman's correlations were used to assess the relationships between behavioral performance metrics and ERP amplitudes, as well as symptom ratings within each group during each time window. Tukey *post-hoc* analyses of statistically significant or relevant main and interaction effects were performed where applicable, with Bonferroni corrections conducted for multiple comparisons. All data are reported as mean and SEM. The level of probability for statistical significance was set at 0.05 and for correlational analyses at 0.01. All statistics were performed using SPSS (22.0, Chicago, USA).

RESULTS

Demographics

The demographics of SZ patients and healthy subjects are shown in Table 1. One-way ANOVAs demonstrated no significant between group differences in age, smoking status, level of education, or handedness ($Fs < 1$, NS), and χ^2-analysis indicated no significant between group gender distributions ($F(1) = 2.09$, $p < 0.13$). These variables were not included in further analyses.

5C-CPT Behavioral Differences

Patients with SZ exhibited significantly poorer overall task performance relative to HCs (sensitivity index (SI)). Patients also demonstrated significantly lower HRs, slower reaction times, and a higher FAR compared with HCs, but did not differ on response strategy (bias) as measured by responsivity index (Table 2 and Figure 3 insets).

Task-Related ERPs

Target trials. MANOVAs of centroid amplitude by group during target trials were completed for each time window. No significant differences for any centroid ERP amplitude between HC and SZ participants were observed during the early time window (100–150 ms; $F's < 2.5$, $p's > 0.05$; Supplementary Figure 1). During the middle time window (150–250 ms), patients demonstrated significantly reduced

Table 2 Between Group Comparisons of 5C-CPT Behavioral Performance of Healthy Comparison (HC) Subjects *vs* Patients with SZ

Performance metric	Group means (SD)		ANOVA		
	HC	SZ	F-value	*p*-value	Cohens *d*
Mean correct RT[a]	318.6 (39.4)	357.6 (60.2)	$F_{(1,49)} = 7.5$	0.01	0.77
Mean incorrect RT	717.7 (264)	741.4 (209)	$F_{(1,49)} = 0.1$	0.73	0.00
HR[a]	0.988 (0.01)	0.975 (0.02)	$F_{(1,49)} = 5.7$	0.02	0.67
False alarm rate[a]	0.00 (0.002)	0.01 (0.007)	$F_{(1,49)} = 6.1$	0.02	0.70
SI[a]	0.99 (0.01)	0.97 (0.03)	$F_{(1,49)} = 7.8$	0.01	0.78
RI	−0.33 (0.27)	−0.31 (0.23)	$F_{(1,49)} = 0.4$	0.85	0.05

Abbreviations: 5C-CPT, five-choice continuous performance task; HC, healthy control; HR, hit rate; RI, responsivity index; SI, sensitivity index; SZ, schizophrenia.
[a]Significant group differences.

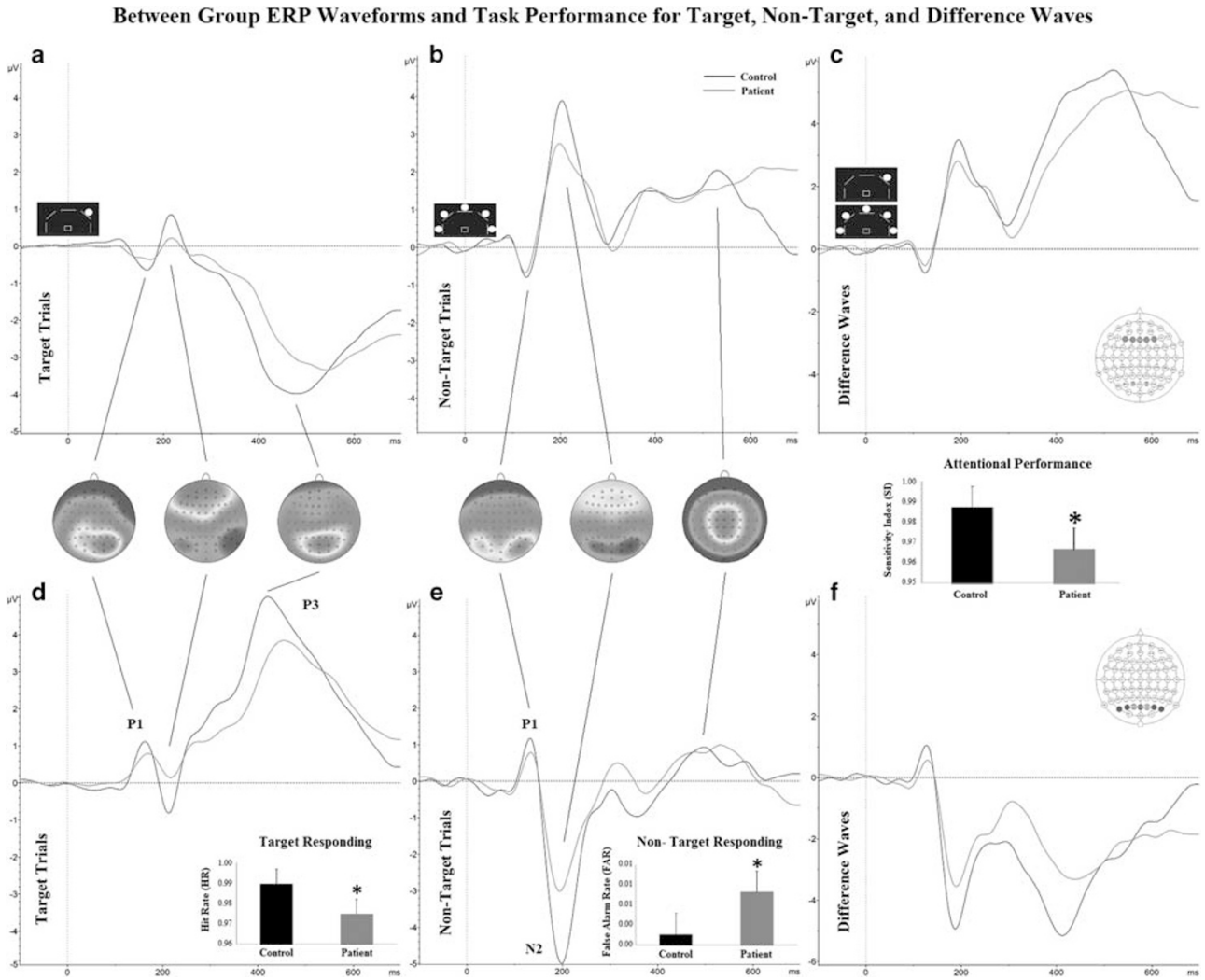

Figure 3 Event-related potential (ERP) and behavioral data. Between group ERP comparisons for target trials (a,d), non-target trials (b,e), and difference waves (c,f) measured at the frontal centroid 3 (top row) and the occipital parietal centroid 8 (bottom row) of healthy participants (control) and schizophrenia patients. The P_1, N_2, and P_3 ERPs are indicated. Inset topography plots show greatest scalp amplitude location for ERP peak. Inset bar graphs indicate between group behavioral performance within conditions, with schizophrenia patients exhibiting reduced target responding (hit rate (HR)), increased response disinhibition (false alarm rate), and impaired vigilance (SI). Behavioral data presented as mean+SEM, $^*p < 0.05$ compared with control. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

ERP amplitudes at centroids one ($F_{(1,50)} = 8.1$, $p < 0.01$), two ($F_{(1,50)} = 7.9$, $p < 0.01$), three ($F_{(1,50)} = 6.5$, $p < 0.02$), six ($F_{(1,50)} = 4.5$, $p < 0.04$), seven ($F_{(1,50)} = 6.4$, $p < 0.02$), eight ($F_{(1,50)} = 7.2$, $p < 0.01$), and nine ($F_{(1,50)} = 5.6$, $p < 0.03$; Supplementary Figure 1). During the later time window (300–550 ms), SZ patients exhibited decreased ERP amplitude compared with controls at centroid eight ($F_{(1,50)} = 6.3$, $p < 0.02$).

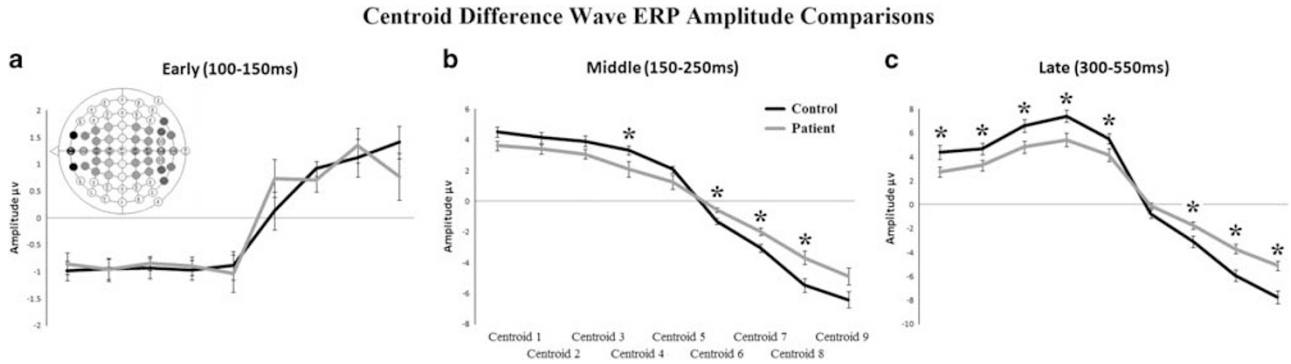

Figure 4 Centroid difference wave amplitudes. The between group centroid difference wave amplitudes and SEM for the early (P_1: 100–150 ms; a), mid (N_2: 150–250 ms; b), and late (P_3: 300–550 ms; c), sensory time window post stimulus onset for healthy comparison subjects (control in black) and schizophrenia patients (in red). *$p < 0.05$ compared with controls. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

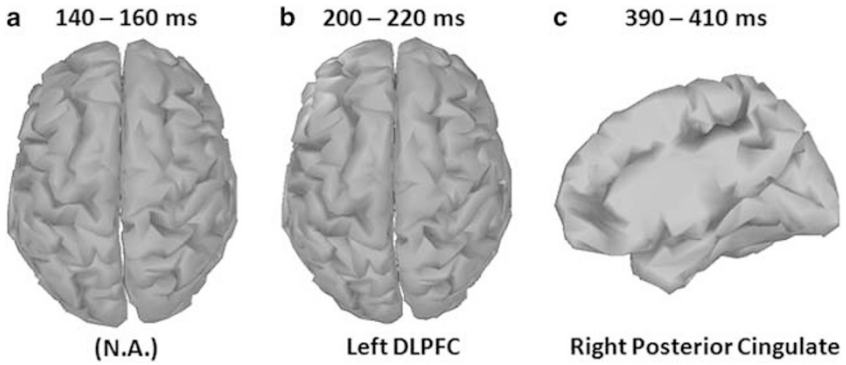

Figure 5 Electroencephalographic (EEG) source analysis for target trials. Cortical maps indicate sources for event-related potential (ERP) peak activation during each time window. No difference between schizophrenia patients and healthy comparison participants were observed early time window (P_1; a). Source localization analyses of the middle time window (N_2) indicated significantly greater positive source activity (current source/efferent dipole), in the dorsolateral prefrontal cortex (DLPFC) for healthy participants compared to schizophrenia patients (b). Source localization analyses also indicated greater negative source activity (current sink/afferent dipole) in the right posterior cingulate cortex in the later time window (P_3) for healthy participants compared with schizophrenia patients (c). Source analyses were computed for the 20 ms (10 ms pre and post) surrounding the group-level ERP peak amplitude for that time window. For both N_2 and P_3 windows, healthy participants demonstrated greater source activity compared to schizophrenia patients, with source colors representing dipole direction of significant between group differences. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

Non-target trials. During the early time window (100–150 ms), SZ patients demonstrated increased ERP amplitude only at centroid six ($F_{(1,50)} = 4.1$, $p < 0.05$; Supplementary Figure 2). During the middle time window (150–250 ms), SZ patients demonstrated significantly reduced ERP amplitudes at centroids one ($F_{(1,50)} = 4.9$, $p < 0.04$), two ($F_{(1,50)} = 4.2$, $p < 0.05$), six ($F_{(1,50)} = 5.2$, $p < 0.03$), seven ($F_{(1,50)} = 7.8$, $p < 0.01$), eight ($F_{(1,50)} = 6.1$, $p < 0.02$), and nine ($F_{(1,50)} = 4.1$, $p < 0.05$) with centroid three at trend level ($F_{(1,50)} = 4.8$, $p < 0.06$; Supplementary Figure 2). During the later time window (300–550 ms), patients demonstrated decreased ERP amplitude only at centroid nine ($F_{(1,50)} = 5.4$, $p < 0.03$).

Difference waves between target and non-target trials. MANOVAs of centroid difference wave amplitudes by group was completed for each time window. No significant between group differences in the earliest (100–150 ms) time window were seen (F's < 2.5, *p*'s > 0.05; Figure 4a). During the middle (150–250 ms) time window however, SZ demonstrated significantly smaller difference wave amplitudes at centroids four (($F_{(1,50)} = 4.5$, $p < 0.04$), six ($F_{(1,50)} = 7.6$, $p < 0.01$), seven ($F_{(1,50)} = 9.1$, $p < 0.01$), and eight ($F_{(1,50)} = 8.1$, $p < 0.01$); Figure 4b). During the later (300–550 ms) time window, SZ patients demonstrated significantly smaller difference wave amplitudes at centroids one ($F_{(1,50)} = 5.2$, $p < 0.03$), two ($F_{(1,50)} = 4.2$, $p < 0.05$), three ($F_{(1,50)} = 5.4$, $p < 0.03$), four ($F_{(1,50)} = 7.1$, $p < 0.01$), five ($F_{(1,50)} = 4.1$, $p < 0.05$), seven ($F_{(1,50)} = 5.2$, $p < 0.03$), eight ($F_{(1,50)} = 13.5$, $p < 0.00$), and nine ($F_{(1,50)} = 15.6$, $p < 0.00$); Figure 4c). No NGA differences were observed between groups (see Supplementary Information and Supplementary Figure 1).

Correlating ERP analyses with behavioral measurements in the later response action time window (300–550 ms). Spearman's correlational analyses were performed to assess the relationships between behavioral performance indices and difference wave ERP amplitudes within the later time window. As difference waves were calculated based on target *vs* non-target ERPs and SI reflected the behavioral differences between target and non-target performance (HR-FAR), we predicted correlations between these measures. Consistent with our prediction, SI correlated with ERPs at centroid eight ($\rho = -0.489$, $p < 0.0001$). When analyzed by group, HC displayed a significant correlation between SI and

amplitudes only at centroid eight ($\rho = -0.523$, $p < 0.008$), with SZ patients not exhibiting significant correlations.

Source Level Results

With the 20 ms average centered over each peak, source data comparison between SZ patients and HC revealed brain regions of significant differences for the second (N_2) and third (P_3) peaks of the target condition (cluster corrected $p < 0.05$). Significant differences were found in the left dorsolateral prefrontal cortex (DLPFC) for the second peak and in the right posterior cingulate cortex for the third peak (Figure 5). The results indicate that the source current density is more positive in HC than SZ patients for the second peak, but less in HC than SZ patients for the third peak. The scout time traces in the localized regions indicate that in both cases, patients had a decrease in signal amplitude. When averaged across the same time windows as in the centroid analysis, the source level statistics demonstrated similar patterns of change without correction (Supplementary Figures 2 and 3).

Exploratory Correlational Analyses

Although these results indicate a biomarker for attentional functioning in SZ, prior research suggests the medial-frontal P_3 may be particularly sensitive to negative symptomotology (Kawasaki *et al*, 2007). Spearman's correlational analyses were performed to assess the relationships between negative symptoms (as measured by the SANS) and centroid P_3 difference-wave amplitudes across the scalp. The Bonferroni correction was used to correct for multiple comparisons, resulting in an α of 0.005. Significant negative relationships were found between P_3 amplitude and SANS total score at fronto-central centroids three ($r = -0.628$, $p < 0.001$) and four ($r = -0.742$, $p < 0.000$) with similar relationships seen at parieto-occipital centroids eight and nine (r's > 0.456, ps < 0.02). However, the parieto-occipital relationships failed to survive correction (Supplementary Figure 4).

DISCUSSION

This study replicates and extends our previous behavioral characterization of 5C-CPT performance deficits in SZ patients (Young *et al*, 2013a). Using ERPs, the present study demonstrated that SZ patients exhibit robust information processing abnormalities even on trials with correct behavioral performance. These abnormalities were localized to regions known to be involved in attentional network, ie, the DLPFC and posterior cingulate cortex (Squire *et al*, 2013). Moreover, these ERP abnormalities were significantly correlated with behavioral performance metrics—stronger in HC than SZ participants—suggesting that impaired stimulus-related information processing may still significantly contribute to subsequent attentional performance deficits.

Patients with SZ exhibited poorer 5C-CPT behavioral performance than HC subjects, driven in part by reduced responses to target stimuli, reproducing earlier reports (Young *et al*, 2013a). In addition, significantly higher non-target responses (indicating response disinhibition of SZ patients) were also observed *vs* a nonsignificant increase previously (Young *et al*, 2013a), possibly as a result of a larger sample size in this study. Hence, consistent with other CPTs (Cornblatt and Keilp, 1994; Cornblatt and Malhotra, 2001; Nuechterlein, 1991), SZ patients exhibited consistently significantly deficient responses in the 5C-CPT irrespective of trial type, not driven simply by an altered response strategy (bias). These behavioral differences are significant with medium to large effect sizes (Table 2), despite a high standard of performance of participants in this task. In addition, the clinical significance of such differences have yet to be determined using standard metrics. In terms of 5C-CPT performance level however, the observed level is not at ceiling given that we have observed significant improvements in human task performance based on motivation, amphetamine, or modafinil (MacQueen *et al*, in preparation; Cope *et al*, in preparation; Bismark *et al*, in preparation). In order to provide varying levels of performance however, a 5C-CPT variant is under development using two levels of trial-type difficulty. This adapted 5C-CPT will also determine whether neural responses reported here will vary based upon difficulty level.

Importantly, the present study identified neural measures of deficient performance of SZ patients. Thus, the 5C-CPT is a compelling probe for quantifying prepotent responses, because of evidence of a higher frontal non-target P_3 compared with target P_3 in HC subjects (Figure 3; Ford *et al*, 2004; Pfefferbaum *et al*, 1985), indicative of assessing the control of attention (Luck *et al*, 2012; Lustig *et al*, 2013), as opposed to conflict monitoring (Gonzalez-Rosa *et al*, 2013). This stronger non-target frontal ERP response is also consistent with our fMRI observations of strong frontal activation during non-target trials (McKenna *et al*, 2013a). Larger amplitude target P_3s compared with non-target P_3s were observed in occipital/parietal regions in subjects performing the 5C-CPT. Importantly, SZ patients exhibited weaker neurophysiological responses compared to HCs irrespective of trial type, particularly in mid and late P_3 time windows, supporting the behavioral data, indicating inattentive/response disinhibition of patients. This effect has been observed previously and suggests that SZ patients did not develop a prepotent response as described (Chun *et al*, 2013; Ford *et al*, 2004). This pattern of deficits was not however seen in patients with bipolar disorder (Chun *et al*, 2013). In addition, frontal and occipital/parietal non-target N_2 waves were also observed, which were also weaker in SZ patients compared with healthy subjects. Interestingly, posterior P_1 (early time window 100–150 ms) were observed in response to both target and non-target trials consistent with other CPTs (Sponheim *et al*, 2006). The P_1 was consistent between trial types and is linked to responses in the visual area. This ERP was the only one that that did not differ between patients with SZ and healthy comparison subjects, consistent with other observations (Sponheim *et al*, 2006), supporting that visual processing of the stimuli was unaffected by the one (target) *vs* five (non-target) visual stimuli and was unaffected in patients. Hence, patients with SZ exhibited weaker ERPs at N_2 and P_3 peaks with stronger frontal non-target *vs* target P_3s observed, whereas the opposite was true for occipital/parietal P_3s irrespective of disease state. Among patients, lower amplitude fronto-central ERPs were related to negative symptoms, with similar but nonsignificant relationships demonstrated at occipital/

parietal centroids. These findings are consistent with altered ERP networks in response to target *vs* non-target stimuli (Wynn *et al*, 2015).

The primary biomarker of impaired performance of SZ patients appeared to be the deficient N_2 ERP, as reduced peaks were observed irrespective of target and non-target trials or in frontal or occipital/parietal regions. P_1 peaks occur in response to the visual stimuli presented (targets and non-targets), with N_2 occurring after visual processing prior to choice selection (P_3s). As ERPs were calculated in response to from correct responses, it is evident that N_2 deficiencies in SZ patients occur as a result of altered information processing reflecting impaired response selections. In fact, the elevated non-target *vs* target N_2 amplitude may provide evidence of the cognitive control required for this task.

Reduced N_2 amplitudes have been recorded in SZ patients performing attentional tasks from auditory (Salisbury *et al*, 1994; Umbricht *et al*, 2006) and visual (Alain *et al*, 1998; Bruder *et al*, 1998) stimuli. Importantly, first-episode SZ patients exhibit reduced N_2 amplitudes (Umbricht *et al*, 2006), which differ from generalized attentional deficits, as patients with posttraumatic stress disorder exhibit elevated N_2 peaks (Galletly *et al*, 2008). As noted above, the temporal window of information processing reflected in the N_2 during attentive processing coincides with middle latency ERPs evoked during passive auditory oddball paradigms reflecting automatic sensory discrimination (ie, mismatch negativity; Light *et al*, 2015). Source analysis of the N_2 suggest that the most significant deficit is localized to the left DLPFC, which has been shown to be a key brain region involved in attention and cognitive functioning, particularly in the attentional network (Squire *et al*, 2013). The neural circuitry of this key region has also been consistently shown to be abnormal in SZ patients during information processing (Barch *et al*, 2001). The present study thus further underscores the contribution of impairments in this transitional window from stimulus registration, which appears to be largely intact in SZ, but cascade forward to the cognitive (N_2) and functional sequelae of the illness.

Source level differences were also observed for the P_3 of the target condition. SZ patients exhibited decreased activity (ie, decreased amplitude of negative peak), in the posterior cingulate cortex during target trials in the P_3 window. The posterior cingulate cortex has been linked to the modulation of attention and conscious awareness (Leech and Sharp, 2014). Given that this activation occurred around the time subjects reacted, this effect could include the feedback they were given in the task. For SZ patients, abnormal posterior cingulate cortical activity was linked both anatomically and functionally via studies showing decreased white matter integrity of the cingulate fasciculus and decreased metabolic activity in the cingulate gyrus (Haznedar *et al*, 2004; Kubicki *et al*, 2003). The decreased source level activity observed herein is both consistent with previous findings and supportive of further development of N_2 differences during 5C-CPT as a translational assay for treatment development.

Smoking status can impact ERPs (Knott *et al*, 1999) and cognitive performance, exerting modest attentional improvements in patients but deleteriously affecting healthy subjects when large sample sizes (>100) are examined (Hahn *et al*, 2012). Smoking status was controlled for in the current study with approximately 36% of SZ and 31% of HC participants were smokers. Smoking status did not interact with any performance measure or ERP responses in the present study and the N_2 and P_3 differences observed provide sufficient neural response parameters that were unaffected by smoking status. Other CPT EEG studies have been conducted, but the 5C-CPT used in the present study offers several advantages to alternative CPTs such as the AX-CPT, CPT-IP, and DS-CPT. First, the 5C-CPT does not include additional cognitive/perceptual demands on performance such as working memory, number matching, or challenging visual perception (Silverstein *et al*, 1998). In addition, the 5C-CPT uses internationally recognized shapes as opposed to culture-specific stimuli, hence, in addition to being a domain pure assessment of control of attention, the task can also conducted in rodents (Barnes *et al*, 2012a, b; Harms *et al*, 2012; Tomlinson *et al*, 2014; Turner *et al*, 2013; van Enkhuizen *et al*, 2014; Young *et al*, 2013a; Young *et al*, 2009; Young *et al*, 2013b; Young *et al*, 2011), enabling more relevant cross-species assessment (Young and Geyer, 2015). This translational utility further increases the value of the behavioral and neurophysiological biomarkers investigated during the current study.

These data support our premise that the 5C-CPT measures the control of attention (suppression of a prepotent response (Ford *et al*, 2004; Luck *et al*, 2012; Lustig *et al*, 2013). Importantly, difference wave amplitudes supported reduced ERP amplitudes at fronto-central and parietal centroids during P_3 and N_2 in SZ patients compared with HC subjects. Finally, correlations between centroid ERPs and primary 5C-CPT performances was observed overall, but with stronger links seen to HC performance compared to SZ patients. Hence, the present study provides biomarkers of impaired control of attention of patients with SZ in the reverse-translated 5C-CPT.

In summary, we observed impaired 5C-CPT performance in patients with SZ compared with healthy subjects. These deficits could have arisen from reduced N_2 amplitudes irrespective of region or stimulus type, in SZ patients. Reduced target and non-target P_3s were also observed in patients with SZ. These biomarkers of attentional deficits are more striking given that these ERPs were taken from only correct trials. Hence, even when responding correctly, patients with SZ do not exhibit as strong a neural response to trials compared to healthy subjects. The temporal precision of EEG and the comparable P_1 ERPs of patients and controls support the premise that the downstream neural processing of stimuli is weaker in patients with SZ compared to healthy subjects. Despite group differences already observed, future clinical studies would benefit from identifying commonalities of genes or environment. Pre-clinical studies could then use that information to create a more complete model of deficits in control of attention (Keeler and Robbins, 2011; Lustig *et al*, 2013; Young and Geyer, 2015; Young *et al*, 2012). With the capability of conducting EEG behavioral studies in mice (Brigman *et al*, 2013; Featherstone *et al*, 2015; Ji *et al*, 2013), genetic, environmental, paradigmatic, and EEG biomarker models (Luck *et al*, 2012) could be combined to enhance targeted therapeutic development (Markou *et al*, 2009).

FUNDING AND DISCLOSURE

In the past 3 years Dr Young and Light's work has been funded by NIDA and NIMH, as well as the US Veteran's Administration VISN 22 Mental Illness, Research, Education, and Clinical Center. Dr Young has also received funding from Cerca Insights and Lundbeck, and has received consulting compensation for Amgen and honoraria from Arena Pharmaceuticals and Sunovian. Dr Light has received consulting from Forum, Astellas, and Boehringer-Ingelheim. Drs Bismark, McIlwain, Mr Grootendorst and Sun, and Ms Zhang report no extra funding sources. This work was supported by NIH grants R01-MH104344, UH2-MH109168, the Sidney R. Baer Jr. Foundation, Brain and Behavioral Research Foundation, and the Clinical Translational Research Institute (CTRI).

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)