



Oscillatory brain dynamics supporting impaired Stroop task performance in schizophrenia-spectrum disorder

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ABSTRACT

The Stroop color-word interference task, prompting slower response to color-incongruent than to congruent items, is often used to study neural mechanisms of inhibitory control and dysfunction in schizophrenia-spectrum disorders. Inconsistent findings of an augmented Stroop effect limit identification of relevant dysfunctional mechanism(s) in schizophrenia. The present study sought to advance understanding of normal and impaired neural oscillatory dynamics by distinguishing interference detection and response preparation during the Stroop task in schizophrenia-spectrum disorders via analysis of behavioral performance and 4–7 Hz (theta) and 10–30 Hz (alpha/beta) EEG oscillations in 40 patients (SZ) and 27 healthy comparison participants (HC). SZ responded more slowly and showed less dorsal anterior cingulate (dACC) theta enhancement during INC trials, less enhancement of dACC-sensorimotor cortex connectivity (theta phase synchrony) during INC trials, more alpha/beta suppression though less enhancement of that suppression during INC trials, and slower post-response alpha/beta rebound than did HC. Reaction time distributions showed larger group and Stroop effects during the 25% of trials with the slowest responses. Poorer theta phase coherence in patients indicates impaired communication between regions associated with interference processing (dACC) and response preparation (sensorimotor cortex). Results suggest a failure cascade in which compromised behavioral Stroop effects are driven at least in part by dysfunctional interference processing (less theta power increase) prompting dysfunctional motor response preparation (less alpha/beta power suppression). Inconsistent Stroop effects in past studies of schizophrenia may result from differing task parameters sampling different degrees of Stroop task difficulty.

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1. Introduction

Impaired executive function is considered a robust feature of psychopathology in schizophrenia-spectrum disorders (SZ) and has been judged a schizophrenia endophenotype (Heinrichs, 2004; MacLeod, 2007; Henik and Salo, 2004; Miller and Rockstroh, 2013, 2016). Impaired executive function is commonly manifested in poor performance on executive tasks, in particular slower responses and more errors in SZ than in healthy comparison participants (HC). However, inconsistent behavioral and neural results raise doubts about the mechanism(s) of executive dysfunction. Interference control measured in the color-word Stroop task is a prominent example of inconsistent effects across

studies. Distinguishing Stroop mechanisms potentially impaired in SZ may point to the locus of executive dysfunction.

1.1. Stroop effects in schizophrenia

Response slowing in cognitive tasks has been related to impaired processing speed (Woodward et al., 2013), impaired response-related processes (Kappenmann et al., 2016), or impaired cognitive processes, in some studies accompanied by altered BOLD or electromagnetic response in function-related cortical regions (e.g., Carter et al., 2012; Fassbender et al., 2014; Lesh et al., 2013; Mayer et al., 2015). Thus, either or both cognitive interference detection and preparation for motor response inhibition may contribute to impaired interference control in SZ.

Disproportional response slowing to color-word incongruence in SZ suggests impaired interference control (Barch and Caesar, 2012; Barch et al., 2009; Boucart et al., 1999; Carter et al., 2012; Laurenson et al., 2015; Moritz et al., 2002). Other studies have not replicated group differences in response slowing to incongruent items even when cortical correlates of interference processing distinguish SZ and HC (e.g., Barch et al., 1999, 2004; Boucart et al., 1999; Henik et al., 2002; Lesh et al.,

Abbreviations: dACC, Dorsal anterior cingulate cortex; CON, Color-word congruence; INC, Color-word incongruence; SZ, Schizophrenia-spectrum disorder patients; HC, Healthy comparison participants; DICS, Dynamic imaging of coherent sources algorithm; ICA, Independent component analysis; LCMV, Linearly constrained minimum variance beamformer approach; MNI, Montreal Neurological Institute brain template.

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2013; Perlstein et al., 1998; Popov et al., 2015; Salo et al., 2001; Westerhausen et al., 2011). Inconsistent results have been attributed to differences in task features (e.g., item-by-item vs. parallel stimulus presentation), performance index (accuracy vs. reaction time), or more variable responding in SZ, which may confound identification of impaired cognitive processes (Fassbender et al., 2014; Kosmidis et al., 2006; Karantinos et al., 2014; Rentrop et al., 2010).

1.2. Neural oscillatory activity during Stroop tasks

Interference control and working memory are related to oscillatory dynamics in the 4–7 Hz theta and 8–12 Hz alpha frequency bands (Bonfond et al., 2017; Ergen et al., 2014; Hanslmayr et al., 2008; Jensen and Tesche, 2002; Sauseng et al., 2009), and abnormal dynamics in both frequency bands are evident in SZ (e.g., Popov et al., 2015; Roux et al., 2012). Numerous studies have suggested a major role for dorsal anterior cingulate cortex (dACC) in interference control, reflected in theta power increase upon incongruent compared to congruent items (e.g., Cavanagh and Frank, 2014; Hanslmayr et al., 2008; Popov et al., 2015; Staudigl et al., 2010). Moreover, Huang et al. (2014) demonstrated communication within a prefrontal-cingulate network for efficient conflict resolution by theta/alpha phase coupling in an auditory Stroop-like task.

In addition to modulation of theta and alpha oscillations as mechanisms supporting working memory, modulation in the 13–30 Hz beta band has been reported in executive function tasks such as WM and attention (e.g., Ray and Cole, 1985; Richter et al., 2017), and this variation was found to be reduced in SZ (e.g., Barr et al., 2010; Dias et al., 2013; Gorashi and Spencer, 2015; Liddle et al., 2016). Given that beta modulation in sensorimotor brain regions has been interpreted as neural support for response-related processes such as selection and preparation (Davis et al., 2012; Engel and Fries, 2010; Jensen et al., 2005; Pape and Siegel, 2015; Van Ede and Maris, 2013; Van Ede et al., 2011; Sherman et al., 2016), impaired beta power modulation in SZ may track impaired cognitive and/or motor response-related facets of executive function as probed in the Stroop task. Results relating beta activity to response preparation in SZ have indicated reduced beta desynchronization over motor cortex prior to response execution in SZ (Dias et al., 2013) and reduced beta desynchronization during, but augmented beta rebound after, visual-motor response execution in SZ (Robson et al., 2015).

1.3. The present study

The goals of the present study were to identify neural mechanisms supporting interference processing and motor response preparation as determinants of Stroop performance and to identify which of those neural mechanisms contribute to impaired performance in schizophrenia-spectrum patients. Inconsistencies in the SZ literature were addressed by analyzing behavioral performance and brain activity as a function of each participant's reaction time (RT) distribution, given long-recognized though often overlooked issues about the confounding impact on group statistics of individual differences in task difficulty (e.g., Chapman and Chapman, 1973). In particular, fluctuation in task-related cognitive processes (such as attention, inhibitory control, goal maintenance) and motor response preparation over time may be masked when averaging across trials. Given that more processing variability and fluctuation over time have been reported in schizophrenia patients, the distribution of performance over trials, its relationship with brain activity supporting task processing, and their contributions to (on average) slower responses should be clarified by examining quartiles from the RT distribution (Rentrop et al., 2010) or trial-by-trial analyses (e.g., Fassbender et al., 2014). Quartile binning as used in the present study facilitates distinguishing between response fluctuations and generalized slowing, widely considered a common feature in schizophrenia.

Oscillatory dynamics in the 4–7 Hz theta and 10–30 Hz alpha/beta ranges were examined as measures of interference processing and response preparation, with the hypotheses:

- (1) Replicating past results, SZ produce slower responses overall and a larger behavioral Stroop effect on RT and accuracy than do HC.
- (2) Theta power tracks those behavioral effects, with stimuli prompting less theta power increase in frontal and cingulate regions in SZ than in HC, especially for incongruent stimuli.
- (3) The literature does not provide consistent guidance as to whether SZ will show (a) less alpha/beta power suppression (as one explanation for their slower RT and larger Stroop RT effect) or (b) decoupling of alpha/beta power and RT (as an alternative explanation). For clarity, we hypothesized the former: alpha/beta power also tracks the behavioral effects, in that there is less pre-response alpha/beta power suppression in SZ than in HC, especially for incongruent stimuli.
- (4) The different functions of dACC and sensorimotor regions contributing to Stroop task performance are reflected in communication between these regions, manifested in theta phase coherence, with SZ showing less connectivity.

2. Materials and methods

2.1. Participants

Forty inpatient SZ were recruited from the regional Center for Psychiatry and diagnosed by experienced senior psychiatrists or psychologists using ICD-10 criteria (demographic and clinical data in Table 1). Exclusion criteria were a comorbid diagnosis of mental retardation (ICD-code F7x) and a history of neurological condition or disorder, including epilepsy or head trauma with loss of consciousness. Twenty-eight met criteria for paranoid-hallucinatory schizophrenia (ICD-10 code F20.0), 10 were diagnosed with schizoaffective disorder (F25), and 2 met criteria for acute polymorphic psychotic disorder (F23). The number of hospitalizations for psychosis varied between 1 and 25, Mean \pm SD of 6.4 ± 5.2 . At the time of assessment all patients were in the post-acute phase and on stable neuroleptic medication regimen for at least 1 week, either with atypical antipsychotics or with a combination of atypical and conventional antipsychotics.

The patient sample was compared to a sample of 27 HC recruited informally among the university student pool and the local community to be demographically comparable to the patient sample. They were screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) to exclude psychiatric and neurological disorder. The groups did not differ in gender balance or age. HC had marginally more education and higher IQ (see Table 1). All participants had normal or corrected-to-normal vision. Based on the Edinburgh Handedness Questionnaire (Oldfield, 1971), one HC was ambidextrous (laterality quotient >60), and two HC were left-handed ($F(1,65) = 3.67, p = 0.06$). The study was approved by the Institutional Review Board of the University of Konstanz. The responsible clinician verified that the patient was in a sufficiently improved state to provide written informed consent and understand test and interview questions. Participants provided written informed consent prior to the study and received 30 Euro at completion.

2.2. Stimuli and procedure

The present Stroop task was adapted from Popov et al. (2015), Hanslmayr et al. (2008), and Silton et al. (2010). Participants were instructed that they would see a sequence of single words presented in 1 of 3 ink colors (red, green, or blue) on a black screen, separated by a white cross. They were instructed to ignore word meaning, which could match the color or not, and respond to indicate the ink color of each stimulus as quickly and accurately as possible by button press.

Table 1
Demographic and clinical information.

	Age M ± SD (range)	Gender M/F	Education M ± SD (range)	IQ M ± SD (range)	PANSS positive M ± SD (range)	PANSS negative M ± SD (range)	PANSS general M ± SD (range)	CPZ M ± SD (range)
SZ <i>n</i> = 40	35.0 ± 11.1 (18–58)	26/14	11.9 ± 0.6 (7–14)	105.8 ± 14.6 (85–136)	17.0 ± 5.4 (9–32)	19.1 ± 5.4 (9–29)	35.4 ± 8.5 (20–61)	499 ± 324 (50–1300)
HC <i>n</i> = 27	34.5 ± 11.2 (18–68)	17/10	12.5 ± 0.8 (10–13)	115.5 ± 14.8 (94–145)				
Group test	F(1,65) = 0.04 n.s.	$\chi^2(1) = 0.03$ n.s.	F(1,65) = 3.33 <i>p</i> = 0.073	F(1,64) = 8.99 <i>p</i> = 0.004				

Note. Education = number of school years. IQ assessed via Mehrfachwahl-Wortschatz-Intelligenz test form B (MWT-B), a standard German test for premorbid intelligence; data from one HC missing.

Medication: For chlorpromazine-equivalent dosages (CPZ), data of *n* = 6 SZ missing.

N = 20 patients were on atypical neuroleptics only, *n* = 3 on typical only and *n* = 11 received a combination of typical and atypical neuroleptics. Atypical neuroleptics include clozapine, olanzapine, quetiapine, paliperidone, risperidone, aripiprazole, haloperidol, thioxanthene, amisulpride/benzamide were selected as typical neuroleptics.

They were asked to keep their eyes fixated on the white cross or the word in order to minimize eye movements. Fixation cross and words were presented on a black screen 100 cm from the eyes.

Each trial began with the fixation cross presented for 2100 ± 500 ms, followed by word presentation for 2000 ms. In the congruent condition, the German word “rot” (red), “grün” (green), or “blau” (blue) appeared in the corresponding ink color. The incongruent condition presented the same color words written in one of the other colors. The neutral condition comprised German adjectives “nah” (near), “echt” (true), or “mild” (mild) selected from WebCelex to meet the criteria of (a) adjective word class, (b) single syllable, (c) ≤ 4 letters, (d) 100–1000 frequency per million, (e) not a phonological neighbor of any of the three color words, and (f) not sharing initial letters with the color words. Neutral words were printed in red, green, or blue ink.

Across three blocks of 240 trials each, words were presented in pseudorandom order to avoid conflict adaptation, with the restriction that two incongruent trials did not follow each other. The 720 trials included 180 congruent, 180 incongruent, and 360 neutral trials. As hypotheses focused on the Stroop effect (incongruent minus congruent trials), data from neutral trials were not analyzed.

2.3. Task performance measurement

RT in ms were obtained for button presses with index, middle, or ring fingers of the dominant hand on three color-marked buttons (red, green, blue) on a computer keyboard. Responses 300 to 2000 ms after stimulus onset were considered correct or errors, and other responses were excluded from analyses as misses (see Table 2 for number of trials per category in the two groups). Behavioral performance measures (RT and percent correct responses of total trials per condition) were examined in a 2 × 2 ANOVA with the between-subjects factor Group (HC, SZ) and the within-subject factor Condition (congruent [CON], incongruent [INC]). Moreover, for each participant the distribution of RTs on correct trials was binned into quartiles (<25, 25–50, 50–75, >75%ile) and submitted to a Group × Condition × Quartile ANOVA, with orthogonal

polynomial trend components characterizing the quartile variance, in order to identify possible distributional differences (Fassbender et al., 2014; Karantinos et al., 2014; Rentrop et al., 2010). Additionally, each participant's brain measures extracted from single trials were averaged across trials within his or her RT quartiles. The relationship between behavioral performance and brain activity measures was evaluated using Spearman's correlation (ρ).

2.4. EEG measurement

EEG was measured in an electrically shielded room using a 256-channel HydroCel net (Electrical Geodesics, Inc., Eugene, Oregon, USA). EEG filtered 0.1 to 400 Hz was sampled at 1000 Hz. The Cz recording reference was changed to average reference in offline analyses. Electrode impedances were kept below 30 K Ω , appropriate because of the high input impedance of the EGI amplifiers (Keil et al., 2014). Digitized electrode positions were registered to positions in the ICBM 2009a Non-linear Asymmetric 1 × 1 × 1 mm template brain (Montreal Neurological Institute, Montreal, Canada <http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152Nlin2009>).

Only trials with correct responses (hits) were included in EEG analyses. For each trial, an epoch of 500 ms pre- to 3000 ms post-stimulus-onset was extracted from the continuous data. Artifact control employed independent component analysis (ICA; Jung et al., 2000). Components with topographies evidently representing saccades, eye blinks, or cardiac signals were removed. Groups did not differ in the number of correct, artifact-free trials retained in either of the two conditions (CON: HC M ± SD = 174 ± 7, SZ = 174 ± 12, $t(65) = 0.16$, $p > 0.8$; INC: HC = 168 ± 10, SZ = 168 ± 9, $t(65) = 0.02$, $p > 0.9$).

A windowed Fast Fourier Transform (FFT) was used for each epoch. For frequencies below 40 Hz, a 500 ms sliding window (50 ms steps) multiplied by a Hanning taper was used to ensure an effective frequency resolution of at least ~2 Hz. Power estimates were averaged over artifact-free trials within condition. Change from the 500-ms prestimulus

Table 2
Number of trials with correct responses <2000 ms, incorrect responses <2000 ms, and rejected responses >2000 ms.

	Correct CON	Correct INC	Incorrect CON	Incorrect INC	Rejected CON	Rejected INC
SZ <i>n</i> = 40	176.7 ± 10.8	170.4 ± 7.3	6.1 ± 5.1	6.7 ± 5.5	1.7 ± 2.6	2.6 ± 3.4
HC <i>n</i> = 27	175.7 ± 7.9	169.6 ± 10.2	5.0 ± 5.4	8.6 ± 8.2	0.6 ± 1.3	0.8 ± 1.9
Group effect size	0.103	0.093	0.211	0.283	0.506	0.622
F(1,65)	0.16	0.14	0.72	1.28	4.27	6.38
<i>p</i> =	0.689	0.707	0.399	0.260	0.049	0.014

Note. Mean ± SD. Effect sizes are group differences per Hedges' *g*. Group × Condition ANOVAs on number of trials:

Correct: Group $F < 1$; Condition $F(1,65) = 35.34$, $p < 0.001$; Group × Condition $F < 1$.

Errors: Group $F < 1$; Condition: $F(1,65) = 14.79$, $p < 0.001$; Group × Condition: $F(1,65) = 7.81$, $p = 0.007$.

Rejected: Group: $F(1,65) = 6.45$, $p = 0.014$; Condition $F(1,65) = 4.48$, $p = 0.038$, Group × Condition: $F(1,65) = 164$, $p = 0.205$.

Although SZ had more trials with responses >2000 ms, as a proportion of the number of trials analyzed the difference is too small to have affected other results.

No trials had RTs < 300 ms.

baseline was expressed in decibels (dB). Time-frequency representation of power reflects both evoked and induced power.

2.5. Relationship between task performance and sensor-level data

Spearman's correlations across participants were computed for each electrode, time, and frequency bin. Statistical inference was based on cluster-based permutation tests (see below). Within-subject correlations across trials employed single-trial RTs and EEG scores. If not indicated otherwise, comparisons and thresholds in the statistical images used an alpha level of $p < 0.05$. Reported p -values involving the four-level quartile factor reflect Huynh-Feldt correction.

2.6. Neural communication evaluated for source-level data

Source reconstruction of oscillatory activity was performed with the dynamic imaging of coherent sources (DICS) algorithm (Gross et al., 2001) and time-domain analysis in source space with a linearly constrained minimum variance (LCMV) beamformer approach (Van Veen et al., 1997). DICS uses the sensor-level cross-spectral density matrix and a set of location-specific forward models to construct spatial filters optimized for a given frequency at the specific locations. Data from INC and CON conditions were pooled for spatial filter construction, and the filters were used to determine the spatial distribution of oscillatory activity separately for each condition. Forward models were calculated using a realistically shaped three-layer boundary-element volume-conduction model and a 3D grid of dipole locations with equidistant positions in MNI space (10 mm spacing). Given the head model and the electrode locations, a source (i.e., forward) model per dipole location can be created. This model describes the 'visibility' or topography of a given source at a given location and orientation. For any given contrast reported here, we tested all dipole locations, e.g. voxels, without any pre-selection. We relied on the non-parametric clustering algorithm described above. For those locations, time courses of neural activity were then estimated via LCMV beamforming, such that the spatial filters were multiplied by the data in order to obtain 'virtual channel' time series at the respective locations.

Neural communication between cortical sources of oscillatory activity was quantified via phase synchrony, specifically the imaginary part of coherence (Nolte et al., 2004). This frequency-domain measure of correlation quantifies phase synchrony between two locations avoiding effects of volume conduction (which affects only the real-number portion of the coherence computation and could otherwise exaggerate relationships). Statistical hypothesis testing used a cluster-based approach with Monte Carlo randomization (Maris and Oostenveld, 2007). The general idea is that real neurophysiological effects have specific structure in the spatiotemporal data matrix that can be exploited in order to maximize statistical sensitivity. Due to the temporal and spatial structure of the EEG signal, neighboring time points and electrodes are likely to reflect the same neural phenomena; aggregating these spatiotemporal neighbors into clusters pools the evidence for an effect being present. The spatiotemporal clustering is combined with a permutation framework to generate a distribution of expected cluster-based test statistics, with the null hypothesis of exchangeability of the data across conditions or experimental groups. In this way, a large number of

statistical evaluations, as is common in a mass univariate context, is reduced to a single statistical evaluation, thereby controlling the family-wise error rate. Specifically, Monte Carlo approximation of the randomization distribution for a chosen test statistic was applied. A sample-specific t -statistic was used, 1000 samples of which were produced and formed the randomization distribution of the test statistic. The probability of falsely rejecting the null hypothesis was $p < 0.025$, corresponding to a false alarm rate of 0.05 divided by 2 in a two-sided test. The Monte Carlo estimate identifies clusters of activity on the basis of which the null hypothesis can be rejected while controlling for multiple comparisons. The cluster-based permutation method was applied to all contrasts on scalp and source levels.

3. Results

3.1. Behavioral performance

Consistent with the first hypothesis, Table 3 shows that SZ responded more slowly than HC (Group $F(1,65) = 18.98, p < 0.001$). Inconsistent with the first hypothesis, the Stroop effect (Condition $F(1,65) = 185.26, p < 0.001$) was not larger in SZ (Group \times Condition $F < 1$). Fig. 1 (upper right) indicates that in the RT quartile analysis both Group and Condition effects were larger on slower trials, reflected in all three of the orthogonal trends moderating each main effect, though essentially a linear effect (see Table 4).

Table 3 shows that, while SZ responded more slowly, they were no less accurate than HC overall (Group $F < 1$). Across groups, error rate was low but higher on INC than CON trials, as expected (Condition, $F(1,65) = 17.02, p < 0.001$). Contrary to hypothesis 1, HC showed a larger Stroop effect on error rate than did SZ (Group \times Condition ($F(1,65) = 7.64, p = 0.007$), though the absolute differences in numbers of errors was small.

3.2. Oscillatory dynamics

From pre-stimulus baseline, both groups showed an increase in theta power as well as suppression of alpha/beta power 200–1000 ms into INC trials (Fig. 2 top and middle rows). Descriptively, both the increase in mid-frontal theta power and the simultaneous suppression of left-central sensorimotor¹ alpha/beta power were larger in HC than in SZ (Fig. 2 bottom row). Supporting hypothesis 2, SZ produced significantly less INC-trial enhancement of theta than did HC in dACC and superior frontal gyrus (Fig. 2 bottom row left). Alpha/beta suppression is considered in the next section.

3.3. Alpha/beta suppression and behavioral performance

Fig. 1 (bottom row) shows more overall alpha/beta suppression after stimulus onset during trials with longer RT (linear Quartile ($F(1,65) = 56.24, p < 0.001$; 94% of the Quartile variance). Alpha/beta suppression showed the same main effects of Group and Condition that RT did. SZ showed more alpha/beta suppression than did HC (Group $F(1,65) = 13.33, p = 0.001$), and INC trials prompted more alpha/beta suppression than did CON trials (Condition $F(1,65) = 26.62, p < 0.001$).

In support of hypothesis 3, two interactions emerging in the Group \times Condition \times Quartile analysis qualify the Group and Condition main effects on alpha/beta power. A Group \times Condition interaction ($F(1,65) = 5.44, p = 0.02$) reflected a smaller Stroop effect on alpha/beta suppression in SZ ($d = 0.14$; $F(1,39) = 5.25, p = 0.03$) than in HC ($d = 0.26$; $F(1,26) = 21.69, p < 0.001$). A Group \times Condition \times linear Quartile effect ($F(1,65) = 4.44, p = 0.04$; 62% of the Group \times Condition \times Quartile variance) confirmed the impression in Fig. 1 (bottom right) that

¹ Because of the contralateral (to response hand) dominance of this bilateral central beta activity prior to response execution, Pape and Siegel (2015) labeled the region sensorimotor, done here as well.

Table 3
Reaction times and error rates.

	RT CON	RT INC	% errors CON	% errors INC
SZ $n = 40$	729.6 \pm 117.8	815.2 \pm 134.3	3.4 \pm 2.8	3.8 \pm 3.4
HC $n = 27$	594.5 \pm 95.8	687.0 \pm 141.5	2.8 \pm 3.0	4.9 \pm 4.7
Group effect size	1.239	0.933	0.203	0.280
$F(1,65) =$	24.52	14.08	0.67	1.28
p	<0.001	<0.001	=0.415	=0.262

Note. Mean \pm SD, RT in ms. Effect sizes are group differences per Hedges' g .

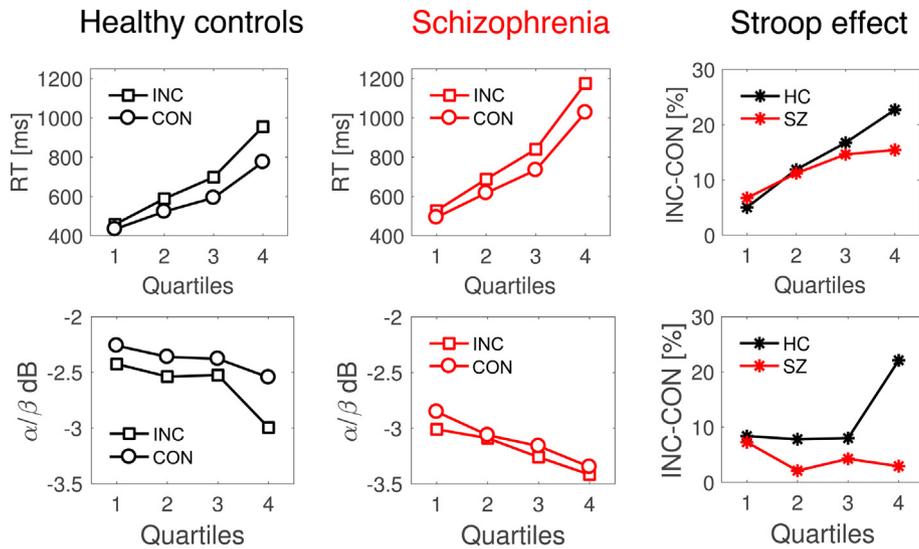


Fig. 1. Top row: mean RT by quartile computed from individual participants' RT distribution. Bottom row: mean alpha/beta power on trials grouped according to the RT quartiles in the top panels. Right column: Stroop effect as percent increase in RT or decrease in sensor-space alpha/beta power [$100 * (\text{INC} - \text{CON})/\text{CON}$] as a function of quartile.

SZ (SZ simple effects: linear Quartile $p < 0.001$; Condition \times linear Quartile $p = 0.53$) failed to show the additional alpha/beta suppression particularly during the slowest INC trials that HC did (HC simple effects: linear Quartile $p < 0.001$; Condition \times linear Quartile $p = 0.04$).

Fig. 3 shows that higher central alpha/beta power suppression varied with longer RT during both INC and CON trials in both groups (INC: HC $\rho = -0.65$, $p < 0.001$; SZ $\rho = -0.70$, $p < 0.001$; CON: HC $\rho = -0.54$, $p < 0.01$; SZ $\rho = -0.81$, $p < 0.001$). A test of homogeneity of regression ($F < 0.5$) confirmed the similarity of the groups.

The somewhat parallel Group and Condition main effects on RT and alpha/beta suppression suggest a relationship between these measures. To evaluate a potential mediating role of alpha/beta power modulation in the Stroop effect on RT, Fig. 4 plots the time course of each participant's alpha/beta power change during a trial, with participants ordered vertically by mean RT. For a given participant, mean alpha/beta power suppression (blue) generally ended about the time of mean RT. (No such relationship was found between theta modulation and RT.) This close tracking of RT by alpha/beta power (see also Fig. 3 scatterplots) suggests that alpha/beta power mediated the RT effects.

However, the right panels of Fig. 4 suggest that the temporal relationship between the time course of alpha/beta power modulation and RT was much less consistent in SZ, with alpha/beta power suppression not terminating at RT so precisely. This was evaluated with a Group \times Condition \times Time ANOVA comparing alpha/beta power at the time of each participant's RT vs. alpha/beta power

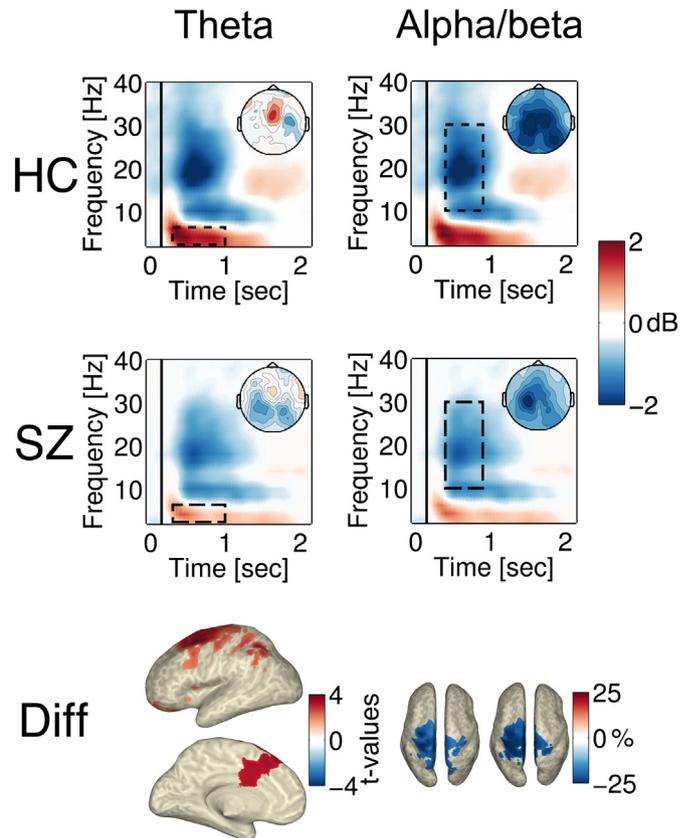


Fig. 2. Top and middle rows: sensor-space time-frequency representation of power (TFR) during INC trials averaged over central electrodes (word onset at 0 on X axis). For simplicity, results for INC trials are shown, to illustrate group differences by frequency band and to foreground group differences in the Stroop effect (INC minus CON) shown in the bottom row. CON-trial time-frequency distributions did not differ. Warm and cold colors represent power change from prestimulus baseline in dB. Left and right panels present the same TFR information. Within each panel, upper right insets illustrate the scalp topography for activity in the dashed rectangles (left, theta; right, alpha/beta). Bottom row: source-space INC-trial power change from baseline minus congruent-trial power change from baseline scaled to percent of congruent-trial power change from baseline: [$100 * (\text{INC} - \text{CON})/\text{CON}$]. Left: t-map of areas of group difference in theta source power, warm colors indicating SZ < HC. Right: alpha/beta source power distribution for HC (left) and SZ (center) thresholded to show voxels with at least 80% reduction from prestimulus baseline (descriptive only; groups did not differ reliably in Stroop effect on alpha/beta source power).

Table 4
RT quartile interactions with group and condition.

Group \times linear Quartile	F = 20.83, $p < 0.001$	94% of the Group \times Quartile variance
Group \times quadratic Quartile	F = 11.55, $p < 0.001$	6% of the Group \times Quartile variance
Group \times cubic Quartile	F = 8.75, $p < 0.001$	0.4% of the Group \times Quartile variance
Condition \times linear Quartile	F = 96.16, $p < 0.001$	99% of the Condition \times Quartile variance
Condition \times quadratic Quartile	F = 4.38, $p = 0.04$	1% of the Condition \times Quartile variance
Condition \times cubic Quartile	F = 5.40, $p = 0.02$	0.003% of the Condition \times Quartile variance

Note. All F-tests with 1 and 65° of freedom. The Group \times Condition \times Quartile effect did not approach significance ($p = 0.290$), nor did any of its orthogonal trends ($p > 0.12$).

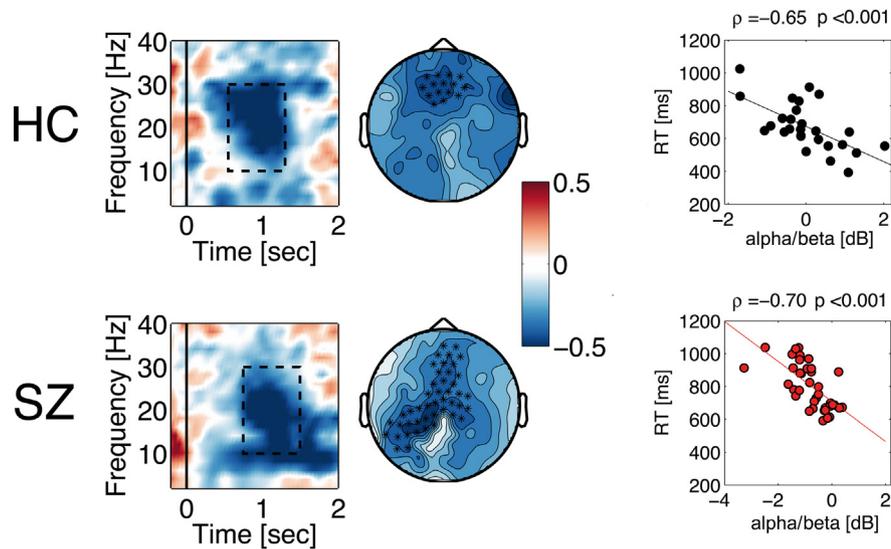


Fig. 3. Left panels: correlation between RT and sensor-space time-frequency representation of power (TFR) during INC trials by time and frequency (word onset at 0 on X axis). Middle panels: Topographic maps show distribution of correlations for the time-frequency tiles marked by the dashed rectangles in the left panels (alpha/beta). Black circles represent the electrode cluster contributing to significant relationships. Color bar is correlation. Right panels: correlation of RT and change in alpha/beta power in those time-frequency tiles. Each black circle represents one participant.

200 ms later. Alpha/beta power did rebound quickly after button-press (Time $F(1,65) = 102.21, p < 0.001$) but less so in SZ (Group \times Time $F(1,65) = 3.84, p = 0.05$).

3.4. Theta-mediated neural connectivity

Communication between dACC and sensorimotor cortex, quantified as theta phase coherence, was significantly higher for INC than for CON words during 500–800 ms (approximately the time of button-press). The dashed rectangle in Fig. 5B indicates when this INC vs. CON phase coherence difference was significantly larger in HC than in SZ. In line with hypothesis 4, Fig. 5C illustrates the role in task performance of theta phase coherence between dACC and sensorimotor cortex. HC showed an association of higher phase coherence and higher RT ($\rho = 0.42, p < 0.05$). SZ did not ($\rho = -0.14, p = 0.38$; test of regression slopes $p = 0.001$).

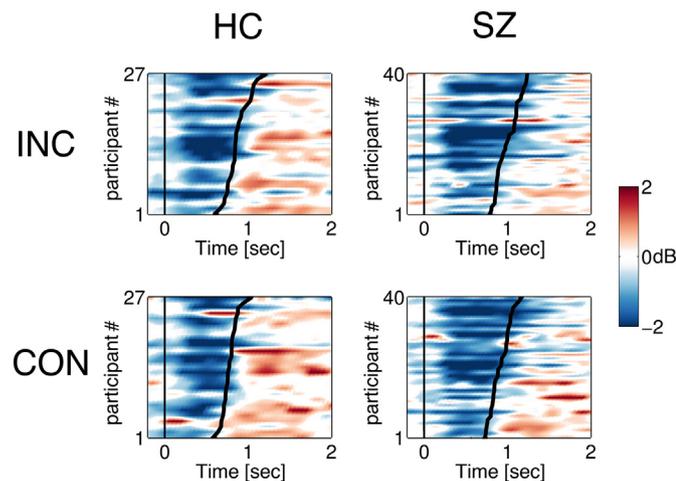


Fig. 4. Time courses of individual participants' sensor-space alpha/beta power changes from baseline (word onset at 0 on X axis). Each row is one participant, ordered by individuals' mean RT (thick near-vertical black line). Warm colors reflect an increase and cold colors a decrease in 10–30 Hz power from baseline.

4. Discussion

The present study sought mechanisms of interference detection and motor response preparation as potential contributors to Stroop performance and to the inconsistent reports of impairment in SZ, using brain oscillatory dynamics to evaluate regional processes and inter-regional communication. Hypotheses were developed to understand Stroop impairment in SZ and contributions to its variation across studies.

Present behavioral and neural effects emerged even though the first hypothesis received only partial support, in that SZ responded more slowly overall but not more so during INC trials and not less accurately than HC. A key behavioral finding (Fig. 1 top row) was that patients' slower RT (per hypothesis 1) was carried by individuals' slower trials, not particularly by INC trials. This pattern suggests one explanation for the heterogeneity of findings in the SZ Stroop literature: perhaps in part due to the widely recognized heterogeneity of SZ samples across studies, inconsistent results may reflect studies diverging in their sampling of individuals' cognitive and motor performance space. This issue is sometimes addressed a priori by inclusion of a battery of tasks. That ambitious undertaking faces major psychometric challenges that individual studies almost never address (Chapman and Chapman, 1973; Nuechterlein et al., 2008). Furthermore, reliance on a standardized procedure for each task in the battery does not address the problem that individual patients vary in capacity on that task and perhaps differentially across tasks. The present approach involved systematically exploring performance on a single task, thus avoiding some of the psychometric challenges. That strategy limits generalizability, but the goal was to address the inconsistency of findings in the SZ Stroop literature, rather than a comprehensive representation of cognitive impairment in SZ. What some studies have reported as Stroop effect enhancement in SZ may simply reflect INC trials pushing SZ further along some performance-parameter dimension, rather than a deficit specific to Stroop processing. Alternatively, observation of Stroop-specific impairment may depend on specific task parameters positioning SZ on such a dimension.

Turning to the goal of identifying neural mechanisms contributing to SZ impairment, several abnormalities emerged. Present findings replicated smaller frontal theta power increase during INC trials in SZ, supporting the second hypothesis and the notion of inadequate interference processing in SZ. Contrary to the third hypothesis, rather than a

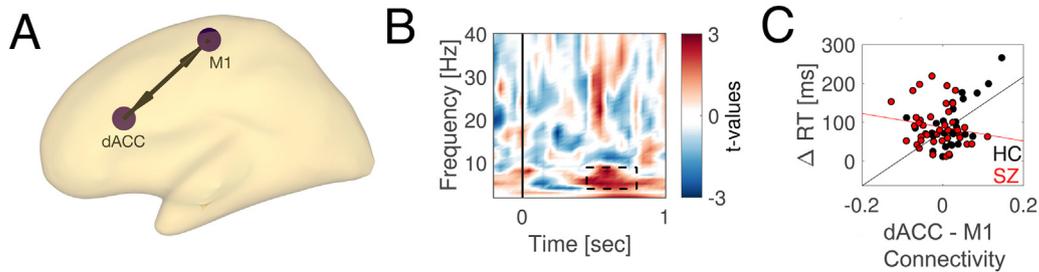


Fig. 5. A: Locations of voxels in coherence analysis. dACC: dorsal anterior cingulate cortex. M1: primary sensorimotor cortex. B: Group \times Condition interaction effect (INC_{HC} minus CON_{HC} vs. INC_{SZ} minus CON_{SZ} , per t-value color bar at right) on source-space phase coherence as a function of time and frequency (word onset at 0 on X axis). Warm colors indicate larger INC minus CON difference in phase coherence in HC than in SZ. The dashed rectangle marks the time-frequency window used in 5C. C: Relationships between Stroop effect on RT (INC minus CON) and Stroop effect on source-space dACC-M1 connectivity (INC minus CON) measured as theta-phase coherence for each group. X axis is INC minus CON difference in coherence. Each circle represents a participant. Black (HC) and red (SZ) regression lines illustrate the significant relationship in HC but not in SZ.

general failure of alpha/beta suppression, SZ showed more alpha/beta suppression overall than did HC (Fig. 1 bottom left vs. middle). Yet SZ also failed to produce additional alpha/beta suppression during the slowest INC trials (Fig. 1), possibly a floor effect: comparison of the bottom left and bottom middle panels in Fig. 1 reveals that SZ suppression was as severe in all eight conditions as HC reached only for their slowest INC trials. The scatterplots of Fig. 3 show that SZ had the same relationship between alpha/beta suppression and RT as HC, so that linkage was intact. Because Fig. 4 demonstrates that, in HC, termination of that suppression coincides with overt responding (button press), SZ alpha/beta suppression control failure appears to account for their poor overt responding.

As illustrated in Fig. 4, the temporal extent of alpha/beta suppression shows high interindividual variability and less within-subject temporal precision in SZ. Matzke et al. (2017) related longer RT in SZ in a stop-signal task to “slower initiation of inhibition, implicating a failure of attention rather than a deficit in the inhibitory process itself” (p. 1078; see also West and Alain, 2000, Zhao et al., 2015). Melcher et al. (2014) suggested that more response slowing on INC trials in a shape task indicates specifically accentuated conflict processing on top of a general performance deficit in SZ. Cognitive control supported by frontal cortex, evident in low-frequency oscillations, is considered a major factor in attention mechanisms affecting Stroop performance (Tang et al., 2015). The present group differences in theta power modulation and frontal-sensorimotor connectivity suggest the involvement of impaired frontal control in general and/or more fluctuating task performance in SZ (in line with Minzenberg et al., 2009; Lesh et al., 2013). Thus, increasing processing demands over time in tasks that challenge frontal control and attention may reveal impairments that become evident in increasing or more fluctuating responses. In HC, this challenge over time was evident in accentuated alpha/beta suppression and RT Stroop effect in SZ by increasing the overall larger alpha/beta suppression and smaller alpha/beta Stroop effect associated with response slowing. Thus, the pattern revealed by quartile binning suggests such response fluctuation as an important factor in SZ Stroop deficits.

Low dACC-sensorimotor connectivity in SZ during incongruent trials (supporting the fourth hypothesis) suggests that impaired motor preparation is in turn a consequence of impaired interference processing. Theta may be considered a means of communication between dACC (detecting the need for control) and sensorimotor cortex (adapting output to task demands) as a part of larger network engaged by this task (Spielberg et al., 2015). Thus, both dACC-sensorimotor connectivity and alpha/beta power modulation within sensorimotor cortex appear to contribute to the Stroop performance and to SZ performance anomalies.

Among several limitations, use of a single task constraints generalization to other contexts. However, that SZ performed as accurately as HC is evidence that present results are not an artifact of a generalized deficit that complicates interpretation in many SZ studies. The alpha/

beta suppression rebound analysis was undertaken after inspection of the data and warrants replication. Medication remains a potential limitation. Beta activity can vary with dopamine levels (Jenkinson and Brown, 2011), neuroleptic medication, and GABA levels (Prokic et al., 2015) that benzodiazepines affect, although it is not known that these effects extend to connectivity measures, and effects of benzodiazepines on beta activity during motor tasks have not been consistently reported in humans (Fortunato et al., 2015). Just two of the present 40 SZ received mild benzodiazepines (lorazepam). Although an impact of medication on the oscillatory dynamics described for SZ cannot be ruled out, it seems an unlikely contributor.

In summary, poorer phase coherence in SZ suggests a mechanism of impaired communication between regions associated with interference processing (dACC) contributing to impaired response preparation (sensorimotor cortex). Inconsistent Stroop effects in past studies of schizophrenia may result from differing task parameters sampling different degrees of Stroop task difficulty.

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Contributors

BR, TP, and GAM designed the project and this study, BR was responsible for subject/patient recruitment and supervised data collection together with TK, TP and TK set up the experimental protocol and EEG measurement, TP, PP and TK analyzed the data, BR, GM, and TP prepared the manuscript.

Conflict of interest

None of the authors declares any financial, personal, or institutional conflict of interest.

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