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Aberrant connectivity during self–other source monitoring in schizophrenia

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ABSTRACT

Numerous investigations into schizophrenia have reported impairment in self–other source monitoring, and studies on healthy subjects have suggested that the medial prefrontal cortex (mPFC) is a critical region underlying self-monitoring abilities. In the current study, we examined the mPFC-related modulation of other brain regions in schizophrenia during self–other monitoring using a psychophysiological interaction approach. Twenty-three patients with schizophrenia and 33 healthy controls performed a self–other source monitoring task while undergoing functional magnetic resonance imaging (fMRI) scanning. Independent component analysis was used to identify the mPFC region of interest, and the averaged mPFC time course was extracted and entered into a general linear regression model for use with the psychophysiological interaction analysis, with Self vs. Other monitoring being the psychological condition of interest. Results suggested that connectivity between the mPFC and the left superior temporal gyrus (LSTG) was greater in the Other than the Self condition for the healthy subjects, but this was reversed for the schizophrenia patients, such that mPFC-LSTG connectivity was greater during Self than the Other condition. The modified functional connectivity associated with the performance of recollection of self-source information suggests that schizophrenia patients invoke circuits normally involved in retrieving other-generated information when processing self-generated information, thereby providing a possible biological basis for the self–other confusion characteristic of schizophrenia.

1. Introduction

Schizophrenia is a disorder associated with symptoms such as hallucinations, delusions, and thought disorder. Some of these symptoms (e.g., hallucinations and Schneiderian delusions) are considered to be representative of a disorder of "self," involving difficulty in discriminating between information that was self-generated and that originating from others (Bentall et al., 1991). Behavioral research indicates that schizophrenia patients display difficulty monitoring multiple aspects of their inner and outer experiences, such as self–other verbal information (Allen et al., 2007a, 2004; Ditman and Kuperberg, 2005; Laroi and Woodward, 2007), and tactile stimuli (Blakemore et al., 2000), however, the biological basis of this difficulty is not clear.

Neuroimaging studies on healthy people using various forms of self-referential processing have consistently demonstrated that the medial prefrontal cortex (mPFC, broadly corresponding to Brodmann's area [BA] 10) is a key neural correlate for the recovery and subsequent monitoring of stored information. This region has also consistently been found to be involved in reality monitoring and mentalizing tasks (Dobbins and Wagner, 2005; Frith and Frith, 2003, 2006; Simons et al., 2005a, 2005b) and is purported to play a crucial role in reallocating attentional resources to accurately process contextual information (Burgess et al., 2007; Simons et al., 2005a, 2005b). Meta-analytic studies of imaging research relevant to BA 10 revealed a great deal of

Abbreviations: mPFC, medial prefrontal cortex;STG, superior temporal gyrus;PPI, psychophysiological interaction.

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functional specialization within this region (Gilbert et al., 2006a, 2006b) and led to the proposal of a "gateway hypothesis," which posits that the mPFC influences the attentional balance between self-generated and external information (Burgess et al., 2007; Simons et al., 2005a, 2005b). Disruption in these circuits may thus be attributable to aberrant mPFC-related modulation of other brain regions during self–other monitoring.

Self–other difficulties in schizophrenia are particularly relevant to schizophrenia symptoms like hallucinations (Woodward et al., 2007), whereby patients report hearing voices while none are present. A difficulty in discriminating externally perceived information from that imagined may result from a deficit in monitoring the self-generation of thoughts (Frith and Done, 1989) or bias towards misattributing internal thoughts to external sources (Bentall et al., 1991; Woodward et al., 2007). Cognitive studies have shown that schizophrenia patients with delusions and hallucinations are impaired in judging the origin of previously encoded stimuli and show particular difficulty in identifying the source of self-generated information (Danion et al., 1999; Keefe et al., 2002; Vinogradov et al., 1997). Moreover, a recent study has indicated that abnormal medial prefrontal activation was associated with the inability to discriminate between perceived and imagined information (Simons et al., 2006).

In this functional magnetic resonance imaging (fMRI) study we developed a source monitoring task (based on previous work; Woodward et al., 2007), in which subjects were asked to distinguish between self-generated and externally generated responses. In order to control for potential confounds (e.g., arising from mentalizing, emotional content and task performance, see Gilbert et al., 2006b), a control condition was designed whereby subjects were asked to distinguish between two previously executed tasks: providing semantic associates and reading. This experimental design was similar to the contextual recollection or reality monitoring paradigms used in previous studies (Simons et al., 2005a, 2006, 2008; Turner et al., 2008; Vinogradov et al., 2006, 2008). Given that this event-related design permitted assessment of performance accuracy, the data analysis for the current study focused only on correct trials in order to focus on the abnormal functional connectivity associated with the mPFC during accurate contextual recollection.

Given that the mPFC is a key region in the default-mode network (Gusnard and Raichle, 2001; Raichle et al., 2001) and that this network is often reported to be associated with goal-oriented cognitive tasks (Buckner et al., 2008), in this study we first identify the default network and then extract subject-specific time series from the mPFC for further psychophysiological interaction (PPI) analysis. Pursuant to the gateway theory that suggests a role for the mPFC in maintaining the attentional balance between self-generated and external information, individuals with schizophrenia were expected to show abnormal mPFC functional connections when monitoring self- and other-generated items compared to healthy comparison subjects. Specifically, on the basis of previous relevant studies in functional connectivity (Mechelli et al., 2007), we hypothesized that the impaired connectivity of the mPFC would involve temporal regions sensitive to the judgments of the origin of the source. We also expected that functional connectivity to mPFC in the two cohorts would be equivalent in the task-memory control condition.

2. Materials and methods

2.1. Participants

Twenty-three patients (mean age = 27.3 years, SD = 7.6 years, eight women) were recruited from psychiatric hospitals and community health agencies in and around Vancouver, British Columbia, Canada, with schizophrenia spectrum diagnoses (i.e., schizophrenia, $n = 15$; schizoaffective disorder, $n = 8$). Diagnosis was based on a multidisciplinary team conference during the first month of admission when all sources of information are reviewed. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was administered on the date of MRI testing to confirm diagnosis. Participants were excluded if they had ever suffered a head injury or a concussion resulting in a loss of consciousness for 10 min or more, if they had ever been diagnosed with a neurological disease or illness, or if they had current and/or past problems with substance abuse (including alcoholism). Substance abuse was assessed by chart review and by interview, and participants were also excluded if they met the DSM IV criteria for an Axis I diagnosis of a substance-related disorder (e.g., polysubstance dependence). All patients but one were taking stable doses of antipsychotic medications at the time of testing, with the large majority taking atypical antipsychotics.

Thirty-three healthy controls (mean age = 30.0 years, SD = 9.2 years, 17 women) were recruited through advertisement and word-of-mouth. Screening with a medical questionnaire ensured that none of the healthy participants had any current or prior history of psychiatric illness. Additional exclusion criteria were the same as those employed for the patient groups. All participants gave written informed consent after a full explanation of the study and the procedures involved. All experimental procedures were approved by the University of British Columbia Clinical Research Ethics Board.

2.2. Procedure

The source monitoring task involved a non-scanned encoding session, where 120 to-be-encoded common words were presented sequentially, with 30 words presented in each of four contexts: self-generated (SG), other-generated (OG), association (AS), or reading (RD). The first two contexts (SG and OG) were termed the *source-memory conditions* and were the tasks of experimental interest in this study, whereas the latter two (AS and RD) were the control conditions termed the *task-memory conditions*. On the SG trials, a word puzzle (jumbled letters) was presented on the computer screen in conjunction with a clue about the meaning of the word, and subjects were required to say the word aloud once they had solved the puzzle; on the OG trials, subjects heard a digitized recording of the solution to the puzzle as soon as the puzzle was presented on the screen; on the AS trials, subjects used a keypress to indicate which of two possible words was a stronger semantic associate to the presented word; on the RD trials, subjects read the presented word silently.

Following this non-scanned task session, these words were used as targets during the scanned recall phase. Approximately 10 min after the end of the encoding session,

a 15.5-min recall run was performed while subjects were being scanned. The subjects were informed about the memory component of the task only as they prepared to enter the scanner. The recall run consisted of 120 trials using all the same words presented in the study phase, divided into six alternating blocks (i.e., *source-memory* and *task-memory* blocks) of 20 trials (140 s per block), where the participant was asked to indicate in which encoding condition that word had been previously encountered. During each trial, a single word was presented in the center of the screen with a cue at the bottom of the screen reminding them of the instructions. While a word was being displayed, participants were asked to judge whether the word was read or associated or whether the participant or the computer had solved the puzzle. In all conditions, participants indicated their response by pressing the left or right key on a MRI-compatible response box with their right hand. For each trial, words were presented for a maximum of 5 s; however, the word disappeared from the screen after a response was made, and the screen remained blank for the remainder of the 5-s period. Each trial was separated by a varying inter-trial interval (ITI) of 1, 2, or 3 s, which included a 1-s fixation crosshair. In addition, to avoid multicolinearity (Cairo et al., 2004), a 10-s blank trial was inserted after each block. The word "relax" was presented for the first 9 s of each blank trial, followed by a 1-s cross hair to cue subjects that a new trial was about to begin. Trials were blocked as opposed to randomly presented in order to avoid brain activations and reaction time costs associated with switching tasks (Ruff et al., 2001; Rushworth et al., 2002; Woodward et al., 2006a).

2.2.1. Image acquisition

Imaging was performed at the University of British Columbia's MRI Research Centre on a Phillips Achieva 3.0 T MRI scanner with Quasar Dual Gradients (maximum gradient amplitude 80 mT/m and a maximum slew rate of 200 mT/m/s). The participant's head was firmly secured using a customized head holder. Functional images volumes were collected using a T2*-weighted gradient echo spin pulse sequence (36 axial slices, thickness/gap = 3/1 mm, matrix = 80 × 80, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 240 mm × 240 mm effectively covering the whole brain. Each scan lasted for 920 s and 460 image volumes were obtained.

2.3. Region of interest (ROI)

fMRI data were preprocessed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Specifically, they included corrections for head movements, spatially normalized to an EPI template in Montreal Neurological Institute (MNI) stereotaxic space, resampled to 2-mm cubic voxels and spatially smoothed with a 5-mm full width at half maximum (FWHM) isotropic Gaussian kernel. A high-pass filter of 1/100 Hz was used to remove low-frequency noises. After preprocessing, images from all participants (33 healthy comparison and 23 schizophrenia patients) were concatenated into a 4D file and entered into FSL Melodic ICA software (http://www.fmrib.ox.ac.uk/fsl/index.html). Many studies have demonstrated that the mPFC is a key region in the default network (Gusnard and Raichle, 2001) and the default network is readily (and unambiguously) identified by using independent component analysis (Greicius and Menon, 2004); therefore, spatial independent component analysis was carried out on the concatenated data to decompose the data into 20 components (Garrity et al., 2007), one of which was identified as a default network component. Then a single cluster covering the mPFC was extracted and the averaged subject-specific activity time course in this region was entered into the subsequent analysis as a seed region.

2.4. Psychophysiological interaction analysis

A psychophysiological interaction describes how functional connectivity between brain regions is altered as a result of psychological context or variables (Friston et al., 1997). In order to examine our hypothesis of abnormal functional connectivity in the mPFC in schizophrenia, we created a linear prediction model to characterize the interaction of physiological and psychological variables as follows,

$$y_i = g_p \cdot \beta_p + g_t \cdot \beta_t + g_p \times g_t \cdot \beta_i + e_i.$$

The voxelwise filtered BOLD signal was represented as y_i. The averaged time series in the mPFC was extracted to generate the neuronal signal for the source regions as the physiological variable (i.e., g_p, one column vector) in the PPI. The psychological variable of interest was the contrast between correct SG (1) and OG (−1) trials. The contrast between correct AS (1) and RD (−1) trials was used as a control condition. This regressor with an additional temporal derivative were temporally filtered, convolved with the canonical HRF and entered into the regression model (i.e., g_t, two column vectors). The bilinear term in PPI represents the interaction between the mean-corrected physiological activity and the center-corrected psychological context input (no temporal derivative; i.e., $g_p \times g_t$, one column vector). In this study, this interaction shows areas with significantly different connectivity with the mPFC between the two conditions in terms of the pre-defined contrast between two psychological contexts: AS - RD or SG - OG. Notably, one has to ensure that the interaction term is not confounded with the main effects, i.e., $[g_p \times g_t]^T \cdot [g_p\ g_t] = 0$. The covariate for the interaction was orthogonalized with respect to those of the main effects in order to give priority to the latter. The PPI analysis was performed for each subject, and the resulting images of contrast estimates on the interaction effect (i.e., β_i) were entered into a random effect between-group analysis. A statistical test revealed significant difference at a cluster-based correction ($p < 0.05$) for multiple comparisons using random field theory implemented in FEAT, one of the FSL tools.

3. Results

3.1. Behavioral data

Behavioral performance for the recall session is shown in Table 1 and was analyzed by way of a repeated-measure ANOVA with Condition (solving, hearing, association and reading) as a within-subject factor and Group (patients vs. controls) as a between-subject factor. With respect to accuracy, a significant

Table 1
Mean accuracy and RT data for task-memory (association, read) and source-memory (self-generated, externally presented) for healthy comparison ($n = 33$) and schizophrenia subjects ($n = 23$).

	Healthy comparison		Schizophrenia subjects	
Item (30 trials each type)	Accuracy (SD)	RT (SD), ms	Accuracy (SD)	RT (SD), ms
Association (AS)	0.86 (0.11)	885 (215)	0.72 (0.17)	987 (283)
Read (RD)	0.82 (0.14)	1109 (210)	0.74 (0.20)	1164 (319)
Self-generated (SG)	0.80 (0.13)	825 (192)	0.77 (0.14)	908 (265)
Other-generated (OG)	0.85 (0.14)	990 (227)	0.75 (0.16)	1053 (276)

Group effect was observed, $F(1,54) = 8.63$, $p = 0.005$. No significant effect of Condition, $F(3,162) = 0.44$, $p = 0.72$, or interaction between Group and Condition, $F(3,162) = 2.134$, $p = 0.1$, was observed. With respect to reaction time (correct trials only), the Group effect and interaction between Group and Condition were not significant, $F(1,54) = 1.80$, $p = 0.19$, $F(1,54) = 0.26$, $p = 0.85$, respectively. However, a significant Condition effect was observed, $F(3,162) = 32.91$, $p < 0.001$, whereby reaction times were longer in the OG ($p < 0.001$) and RD ($p < 0.001$) conditions ($M = 1.02$ and 1.14 s, respectively) relative to the SG and AS conditions ($M = 0.87$ and 0.94 s, respectively).

3.2. fMRI data

In the current study we focused on the results obtained from the PPI analysis. Fig. 1 shows default-mode network regions, including the posterior cingulate cortex, bilateral inferior parietal cortex, ventral anterior cingulate cortex and mPFC. When selecting the mPFC as the seed region, with regards to the within group PPI analysis we did not find any significant difference in either of the condition contrasts (SG vs. OG, and AS vs. RD) in each group ($p < 0.05$, corrected). However, the PPI analysis on the source-memory contrast of SG greater than OG found a significant between-group difference in the left superior temporal gyrus (LSTG, peak MNI coordinate: −48, −14, −2; Fig. 2A, $p < 0.05$, corrected). As shown in Fig. 2B, statistical tests of the post hoc ROI analyses ($p < 0.0001$) demonstrated that control subjects showed significantly higher mPFC-LSTG connectivity during OG than SG conditions, and schizophrenia patients showed significantly higher connectivity during SG than OG conditions. No significant differences were observed in between-group difference for the task-memory contrast, RD vs. AS.

4. Discussion

We examined the mPFC-related modulation of other brain regions in schizophrenia during self–other source monitoring using a psychophysiological interaction approach. The results suggested that connectivity between the mPFC and the LSTG was greater in the Other-generated than in the Self-generated condition for the healthy subjects, but this relationship was reversed for the schizophrenia patients, such that mPFC- LSTG connectivity was greater during the Self-generated rather than the Other-generated condition in schizophrenia. The modified functional connectivity associated with the recollection of self-generated information suggests that schizophrenia patients may invoke circuits normally invoked for

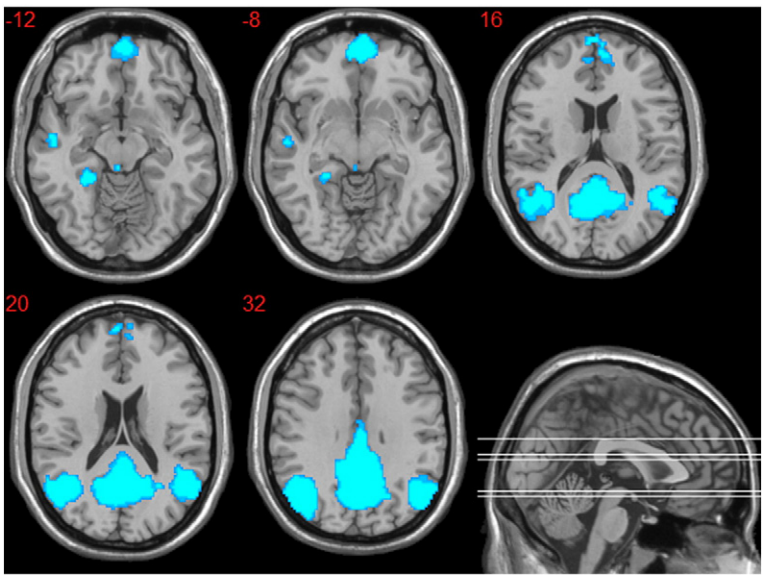

Fig. 1. Default-mode network component for patients with schizophrenia and healthy control subjects. This functional map was identified by a group-level independent component analysis. The number shown in the left top of each panel denotes axial location of each slice in MNI standard space. The left side of each image shows the left hemisphere of the brain.

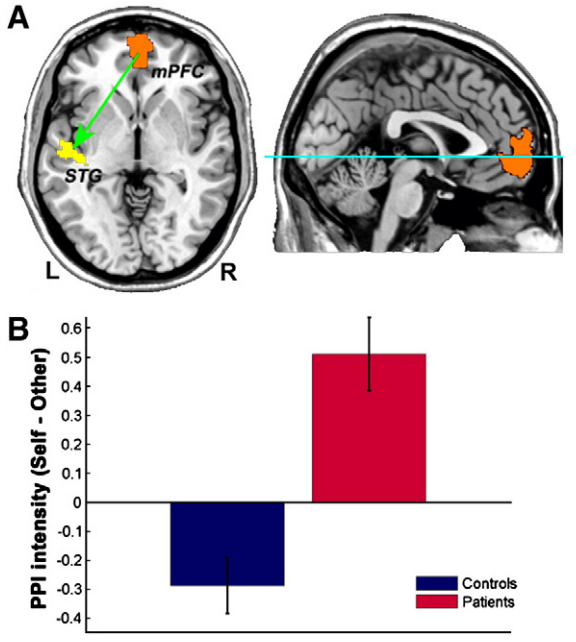

Fig. 2. Changes in functional connectivity with the mPFC in schizophrenia. The PPI analysis revealed that functional connectivity from the mPFC to the LSTG is significantly modulated by source memory condition (A). By averaging the PPI intensity over the voxels within the significant cluster for each subject, a significant interaction effect was found: higher connectivity is observed in the Self condition in patients with schizophrenia, whereas healthy subjects display higher connectivity in the Other condition (B). mPFC, medial prefrontal cortex; LSTG, left superior temporal gyrus.

retrieving other-generated information when processing self-generated information, consistent with previous studies (Mechelli et al., 2007). This finding supports a gateway hypothesis account of the "disorder of self" aspects of schizophrenia (Burgess et al., 2007; Simons et al., 2005a, 2005b), and provides a biological basis for a biased attentional balance between self-generated and other-generated information in schizophrenia.

This study indicated that LSTG interacts with mPFC when evaluating self- and external-generated information. Previous studies have demonstrated altered activity in the superior temporal gyrus and anterior cingulate cortex (which overlaps with the mPFC seed region used in our study) in schizophrenia patients with hallucinations compared with healthy subjects (Allen et al., 2007b). Abnormal activation may thus reflect altered functional integration between the two regions responsible for the appraisal of speech sources. With regards to anatomical connectivity, several non-human primate studies have indicated that these two regions are strongly and directly interconnected (Petrides and Pandya, 1988; Vogt and Pandya, 1987). Furthermore, recent diffusion tensor imaging (DTI) studies in schizophrenia have revealed differences in the orientation of white matter fibers connecting fronto–temporal areas (Hubl et al., 2004; Shergill et al., 2007). The LSTG has been indicated to be more active during the processing of other-generated relative to self-generated speech in healthy controls (Allen et al., 2007b). This region was also associated with auditory hallucinations in schizophrenia in several structural (Levitan et al., 1999; Shapleske et al., 2001) and functional (Shapleske et al., 2001; Shergill et al., 2000b; Woodruff et al., 1997) neuroimaging studies. This finding was line with the previous report of the intrinsic connection between LSTG and the anterior cingulate cortex (Mechelli et al., 2007) and, together, they suggest that the impairment in schizophrenia may be specific to the left hemisphere, which is consistent with reports of a predominantly left hemisphere contribution to the generation of auditory verbal hallucinations (David, 1999; Weiss and Heckers, 1999). This study also provided evidence for altered functional integration within a distributed network of regions in schizophrenia (Fletcher et al., 1999; Meyer-Lindenberg et al., 2005; Shergill et al., 2003; Simons et al., 2006).

The observation of higher mPFC-LSTG connectivity in the Self-generated condition in schizophrenia (more characteristic of that seen in the Other-generated condition in controls) provides support for the notation that aspects of the illness considered a disorder of "self" (e.g., hallucinations and Schneiderian delusions) may be associated with activation in the same parts of frontal and temporal cortices that are normally engaged during perception of external information (Shergill et al., 2000a). This is also supported by studies observing increased fronto-temporal connectivity during the engagement of inner speech (Buchsbaum et al., 2005; Frith et al., 1991). Increased perceptual vividness properties of inner speech during self-generated cognitive events could contribute to the "externalization bias" observed in schizophrenia, whereby schizophrenia patients experiencing self–other confusion (i.e., those experiencing hallucinations and Schneiderian delusions) tend to misremember an internally generated event as originating from an external source (Keefe et al., 2002; Woodward et al., 2006b, 2007). Such a bias would be expected if the neural events that are normally associated with externally generated events are activated during self-generated events (Ditman and Kuperberg, 2005; Laroi and Woodward, 2007; Seal et al., 1997). In addition, the control condition allowed the contribution of task difficulty to be discounted. As mentioned above, behavioral performance results indicated that the OG recall condition was more difficult than the SG recall condition, raising the possibility that the change in connectivity from the mPFC to the LSTG is due to a cognitive load factor. However, no significant PPI effects were observed for the control condition involving the task-memory contrast, RD vs. AS, which was also affected by the same difficulty confound. Overall, these findings may reflect a biased attentional balance between self-generated and external information in schizophrenia (Vinogradov et al., 2008) and may be related aspects of the illness considered a disorder of "self" (e.g., hallucinations and Schneiderian delusions).

This study contained a number of limitations that should be addressed in future work. First, this PPI analysis was based on a relatively small sample, increasing the risk of spurious correlations and precluding the possibility of testing for symptom-specific effects. These results should be replicated on larger sample sizes, and specific associations with hallucinations and Schneiderian delusions require further testing. Second, many theories postulate a great deal of functional specialization within the mPFC (Gilbert et al., 2006a, 2006b; Turner et al., 2008; Volle et al., 2010) along the rostral–caudal, lateral–

medial and dorsal–ventral dimensions. Studies with larger samples could determine which functional subunits play a role in the changes in functional connectivity observed in this study.

These data suggest that the mPFC-LSTG connectivity that is invoked in recalling other-generated information in healthy subjects can be observed when recalling self-generated information in patients with schizophrenia. This may contribute to the inner–outer or self–other confusions that manifest as positive symptoms in schizophrenia such as hallucinations or Schneiderian delusions and suggests that a biological basis for these may involve mPFC-LSTG connectivity.

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Contributors

TSW and PDM designed this experiment in the study. TSW supervised data collection. LW and PDM were involved in the literature searches and data analyses. LW wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None declared.

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