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ORIGINAL PAPER

Influence of empathetic pain processing on cognition in schizophrenia

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Abstract Deficits in both empathy and cognition have been reported widely in patients with schizophrenia. However, little is known about how these deficits interact among such patients. In the present study, we used pain portraying pictures preceding a color-word Stroop task to investigate the effect of empathetic pain observation on cognition among patients with schizophrenia. Twenty patients with schizophrenia and twenty healthy controls were included. The control group showed *increased* Stroop facilitation and *decreased* interference during the empathetic pain condition compared with the non-empathetic condition. Although patients with schizophrenia exhibited deficits in cognition, they demonstrated a similar empathy effect to controls on Stroop facilitation, but a somewhat larger empathy effect on Stroop interference (a more decreased effect). In particular, the groups did not differ in either automatic or controlled processing during the non-empathetic condition, suggesting general rather than specific cognitive deficits in schizophrenia. Together, we interpret our findings in terms of two opposing effects of empathy on cognition in schizophrenia, with possible neuromodulatory mechanism. Whereas prior studies showed empathy to be impaired, our outcomes indicate that at least some components of empathetic pain processing are preserved in such patients.

Keywords Schizophrenia · Empathy · Stroop task · Empathy–cognition interaction

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Introduction

Deficits in empathy and cognition have been consistently reported among patients with schizophrenia [11, 12, 41, 43, 58, 61, 65, 101, 106]. Among these studies, quite a few suggested that impaired cognition could affect empathy. For instance, Bora et al. [12] reported that patients with schizophrenia exhibit deficits in nearly all cognitive tasks, with adverse effects on empathy function. In contrast, few have addressed the question of how empathy might affect cognition in schizophrenia. In the present study, we investigated the interaction between empathy and cognition in schizophrenia by evaluating effects of empathetic pain observation on Stroop facilitation, which reflects automatic cognitive processing, and Stroop interference, which reflects controlled cognitive processing.

Empathy comprises emotional reactions of an observer to the likely affective state of another person [22, 23, 46, 88]. Impaired empathy in schizophrenia has been recognized since the earliest attempts to describe the disorder [56]. Kraepelin described such empathy deficits as "loss of sympathy" and "no share of feelings with others." In

Table 1 Characteristics of patients with schizophrenia and controls

Participants' characteristics	Schizophrenia ($n = 20$)	Healthy controls ($n = 20$)	t value	p value
Age(years)	25.60 (1.26)	21.35 (0.46)	3.16	.003
Gender(female ratio)	8/20	15/20	2.33	.025
Education Level(years)	11.85 (0.63)	15.05 (0.48)	4.01	<.001
Right handedness	19/20	20/20		
Length of illness (years)	5.18 (1.09)			

Standard errors (SE) are presented within brackets

the past, empathy studies in schizophrenia have been conducted primarily by self-assessment or caregiver ratings [7, 12, 21, 70, 79, 90]. Patients with schizophrenia usually exhibit lower scores on trait measures of empathy [10, 24, 102]. However, this line of work may not capture the full scope of, or underlying mechanism of, empathy impairments in schizophrenia. Accordingly, investigators have begun to use performance-based approaches. Such measures suggest affective blunting or inappropriate affective responses, which could be related to deficits in at least three processes underlying empathy in schizophrenia, including (1) affective perception [74, 95], (2) vicarious arousal [45, 67], and (3) cognitive empathy (e.g., [83], for discussion see [12, 90]). These studies demonstrate impaired ability to recognize, share, and/or mimic the internal affective or intentional states of others, such as yawning and laughing resonance [40], facial emotion recognition [25], gesture recognition [107], and eyes test (e.g.,[52], inferring affective states based on eye photographs). Yet, it remains unclear how patients with schizophrenia respond to intense empathetic manipulation and whether or how such manipulations may affect their cognition.

Empathetic pain observation (i.e., viewing others in intense pain) induces a stressful emotional state [69], activates parts of an affective brain network [50, 100], and triggers desires to terminate, reduce, and escape the stimuli [57, 88, 89]. Such reactions are qualitatively different from those observed during more mild empathy manipulations [40, 107]. Our central aim in conducting this study was to assess the interaction of empathetic pain on cognition in schizophrenia, especially how impaired empathy affects controlled and automatic cognitive processing (see it below).

It has been demonstrated that patients with schizophrenia exhibit cognitive deficits in a number of domains, including attention, perception, executive function, memory, and language functions [5, 8, 9, 34, 36, 59, 66, 71, 77, 85, 96, 103]. The discussion is ongoing on whether patients suffer from impaired controlled processing of information (e.g., [18, 44, 91, 94], for a review, see [42, 81]), from impaired automatic processing of information (e.g., [17, 18, 73, 82, 105], but see [3, 6]), or from both. Automatic processing is fast, parallel, difficult to modify, and usually occurs outside of awareness, whereas controlled processing is slow, serial, effortful, and of limited capacity [92, 93, 99]. Empathy may affect these two processes differently in people with schizophrenia.

In the present study, we used empathically painful and non-painful stimuli to manipulate empathy. The stimuli were validated in a pilot study and have been used successfully elsewhere ([37, 38]; see also [50]). To assess the effect of empathy on cognition, especially executive control, we used a standard color-word Stroop task (Stroop [104]; for a review, see [72]). The task was used since it measures the ability to inhibit interference from an over-learned automatic response (i.e., pronouncing a written word, [72, 87, 104]). We assessed both Stroop facilitation and interference effects, which reflect automatic and controlled processing, respectively. Resource models [30, 31, 84] predict a negative effect of empathetic pain processing, since it requires use of central resources. In contrast, attentional facilitation models [14, 15, 29] predict a positive effect on cognition, since empathetic processing narrows attention and screens out irrelevant information. Although these models generate opposing predictions [47, 49], if empathetic pain processing is impaired in patients with schizophrenia, any empathy effect on cognition should be reduced or completely absent, regardless of direction.

Method

Participants

Our sample included 20 individuals who met *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, [2]) criteria for schizophrenia, and 20 healthy controls. Demographic and clinical characteristics are presented in Table 1. The patient group comprised inpatients from Beijing Hui Long Guan Psychiatry Hospital, Beijing China. Patients' diagnoses were confirmed with structured clinical interviews, in accordance with the DSM-IV [33]. Each patient was evaluated by at least two experienced psychiatrists at the hospital. Before conducting the experiments, patients were screened carefully to

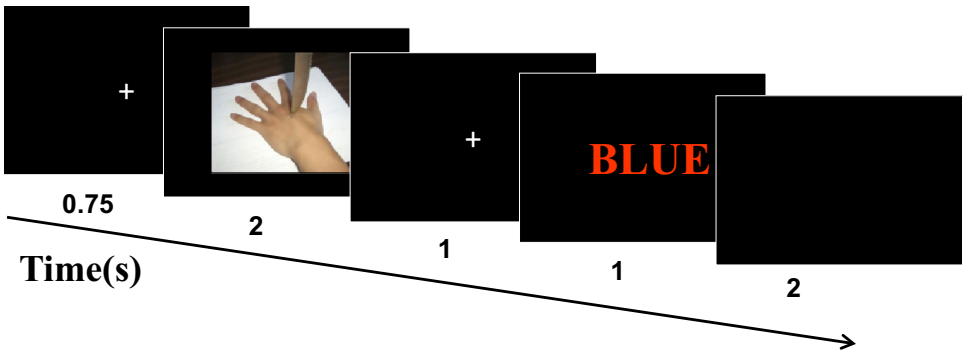

Fig. 1 Task design. The trial began with a fixation display (750 ms), followed by a painful or control (non-painful) stimuli (2,000 ms). After a 1,000-ms interval display, the target appeared for 1,000 ms. During the target period, a Stroop stimulus (a Chinese character in the actual experiment; see text) was presented and involved neutral, congruent, and incongruent conditions (for simplicity, not all task phases are displayed). English word "BLUE" is equal to the character "蓝" in Chinese

rule out disorders that might alter brain functioning, including (1) mental retardation; (2) substance abuse or dependence during the 6 months immediately prior to the study; (3) a history of head injury with documented sustained loss of consciousness, neurological sequelae, or both; or (4) abnormal cerebral metabolism arising from neurological illness or any other disorder. The control group included undergraduate and graduate students recruited from Peking University, Beijing. All participants reported normal or correct-to-normal color vision, and were naïve to the purpose of the experiment. All patients were stable clinically, and most had undergone long-term treatment and were therefore slightly older than the comparison group. All participants gave their oral and written informed consent. The study was carried out in accordance with the guidelines of the Helsinki declaration and was approved by the local ethics committee.

Apparatus and procedure

The experiment was conducted in dimly illuminated rooms. Participants performed a standard Stroop task in which the word was displayed on the screen either in the same color indicated by the word (congruent condition) or in a randomly mismatching color (incongruent condition). Neutral stimuli consisted of a cross (X) in different colors. Throughout the experiment, four colors and their associated color names were presented: 红 ("RED" in English), 蓝 ("BLUE"), 绿 ("GREEN"), and 黄 ("YELLOW"). Each Stroop stimulus (i.e., target) was preceded by an empathically painful or non-painful image (i.e., cue), which depicted incidents that may occur in everyday life. These images were taken from the first person perspective so that participants would not have to perform mental rotation before judging and understanding.[1] Images were slightly blurred with a Gaussian filter to remove any sex or age bias. Painful and non-painful images were identical in physical properties (i.e., context, brightness and contrast, see [37, 38] for further information). Figure 1 shows an example of the sequence of events for a trial. Each trial began with a fixation display for 750 ms. This was followed by an empathically painful or non-painful stimulus display for 2,000 ms. Participants were instructed to passively view these stimuli (no response was required). Following a 1,000-ms interval, a target stimulus containing a colored word or a cross "X" appeared for 1,000 ms. Participants were asked to respond based on the ink color of the word, while ignoring its meaning as quickly as possible, and avoid making too many errors. Finally, each trial ended with a 2-s blank screen. A computer keyboard was directly in front of participants, who used the NumLock keys as the response device.

Five "runs" were included, each consisting of 36 trials. Throughout all runs, painful (empathetic) and non-painful

[1] As described, stimuli were taken from the first person perspective, so observers did not have to perform mental rotation before recognizing the content of images. This may lead to a perspective-taking concern—Would observers have the impression that they are the subject of pain? We used these stimuli in exactly the way Gu et al. [37, 38] and Jackson et al. [50] did. In their neuroimaging studies, they reported significant activation in both frontoinsular (FI) and anterior cingulate cortices. Activation levels of these regions correlated with subjective ratings of dispositional measures of empathy and unpleasantness of pain [50, 100]. Critically, it has been suggested that FI is the most important activation index for the empathy for pain [38]. In the present study, the independent pilot test and the post-experiment debriefing confirmed that observers experienced pain empathy—which was from the third person's perspective. Nevertheless, researchers need to consider the first person perspective possibility in some cases (e.g., with special instruction), and the ability to adopt the other's perspective in some special group (e.g., altruism).

(non-empathetic) trials were intermixed randomly. Trials were balanced between painful and non-painful conditions. Levels of congruency were also balanced, and trials were presented in such a way that no word or color was the same as in the preceding trial, thus minimizing priming effects [76].

Statistical analyses

Correct response reaction times (RTs, in ms) and error rates were computed within each condition, and both main effects and interactions were tested using a 2 (Empathy: painful vs. non-painful) × 3 (Congruency: congruent, neutral, and incongruent) × 2 (Group: patients vs. controls) repeated measures ANOVA. Significant interactions were tested with subsequent ANOVAs or *t* tests, where appropriate. Greenhouse–Geisser corrections were used for all main effects and interactions involving the congruency effect, since it was the only factor with >2 repeated measures and therefore was subject to violations of the sphericity and compound symmetry assumption [51].

Compared with the neutral condition (i.e., the colored "X"), it takes less or more time to identify the color when the color and word are congruent or incongruent, respectively [72, 104]. The decrease in response time when the color of the ink and the word text are congruent is known as Stroop facilitation [$RT_{(Congruent)} - RT_{(Neutral)}$]. In contrast, the increase in response time when the color and the word text are incongruent is known as Stroop interference [$RT_{(Incongruent)} - RT_{(Neutral)}$]. The relative effect of empathy on Stroop interference was calculated by the subtraction ($[RT_{(Incongruent)} - RT_{(Neutral)}]_{painful}$ –$[RT_{(Inongruent)} - RT_{(Neutral)}]_{non\text{-}painful}$), whereas the relative effect of empathy on Stroop facilitation was calculated by the subtraction ($[RT_{(Congruent)} - RT_{(Neutral)}]_{painful} - [RT_{(Congruent)} - RT_{(Neutral)}]_{non\text{-}painful}$). Group effect between Stroop facilitation and interference was tested with independent *t* tests.

Results

Five-point scale ratings of the images (1 = not painful at all through 5 = extremely painful) by 30 independent raters indicate that the painful and non-painful stimuli were significantly different (painful = 3. 45, SD = 1.12; non-painful = 1.13, SD = .40; $t(29) = 20.70$, $p < .0001$, Cohen's $d = 7.69$), validating their affective content. Post-experiment debriefing confirmed that all participants felt that pain was incurred to others when the painful images were presented during experiments.

Response times (RTs)

The data from one participant with schizophrenia (male) were excluded from further analysis because he was left-handed and did not complete the experiment well.[2] All other participants were right-handed. Figure 2 (top panels) displays RTs of correct responses by Stroop condition and group. Reaction time data from correct trials were submitted to a 2 Empathy × 3 Congruency × 2 Group repeated measures ANOVA. Although the main effect of Empathy was not significant, $F(1,37) = 0.08$, $p = .78$, $\eta^2 < .01$, the interaction of Empathy and Congruency was, $F(2, 74) = 10.16$, $p < .001$, $\eta^2 = .22$. The main effect of Congruency was also significant, $F(1,47) = 51.89$, $p < .001$, $\eta^2 = .52$. The three-way interaction of Empathy × Congruency × Group was not significant, $F(2,74) = 1.63$, $p = .20$, $\eta^2 = .04$. In addition, neither the Empathy × Group interaction, $F(1,37) = 2.70$, $p = .11$, $\eta^2 = .07$, nor the Congruency × Group interaction, $F(1,47) = 0.40$, $p = .58$, $\eta^2 < .01$, were significant. However, the main effect of Group was significant, $F(1,37) = 26.12$, $p < .001$, $\eta^2 = .41$, reflecting an overall slower response among patients than controls.

As shown in Fig. 2, RTs in neutral trials were increased during the painful compared with the non-painful condition for both controls, $t(19) = 3.16$, $p < .001$, Cohen's $d = 1.44$,

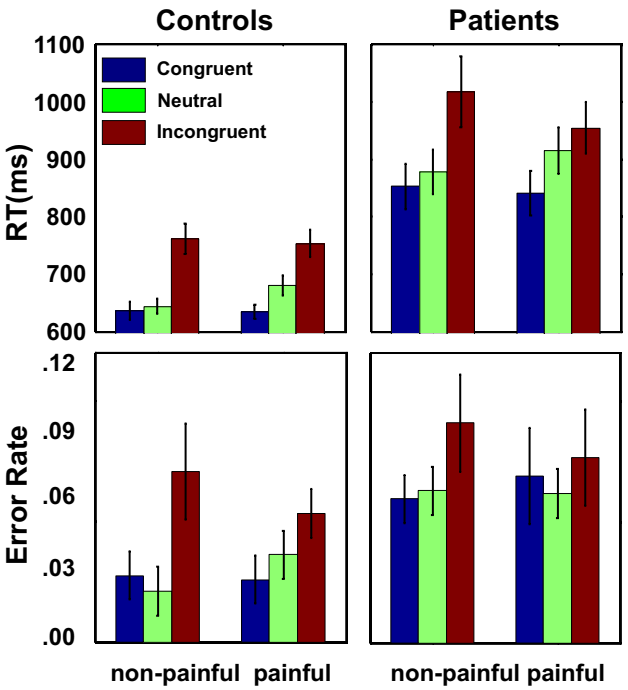

Fig. 2 *Left panel*: data from healthy controls; *Right panel*: data from patients with schizophrenia. *Up row*: reaction times; *Bottom row*: error rates (reported as a proportion). *Error bars* indicate standard errors of the mean

[2] We also conducted data analyses including this participant and results were almost identical.

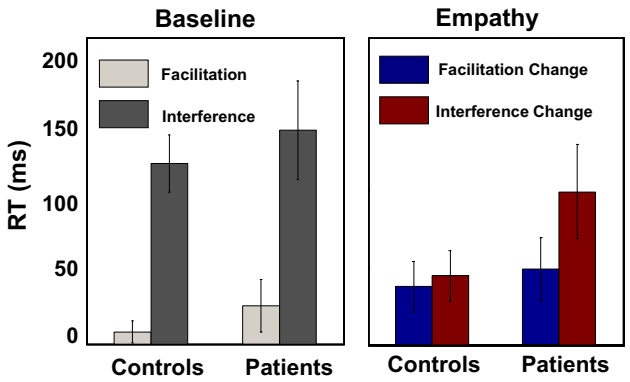

Fig. 3 *Left panel*: Stroop effects under non-painful condition. Facilitation: $RT_{(Neutral)} - RT_{(Congruent)}$; Interference: $RT_{(Incongruent)} - RT_{(Neutral)}$. Both groups showed no difference in either Stroop facilitation or interference effect in the non-empathetic condition. *Right panel*: comparative Stroop facilitation and interference effects (painful vs. non-painful). Note, the comparative Stroop interference change shown here is corresponding absolute values. *Error bars* indicate standard errors of the mean

and patients, $t(18) = 2.60$, $p = .009$, Cohen's $d = 1.23$ (given that all hypotheses were one-directional, we use one-tailed t tests). However, there was no group difference in the effect of empathy, $t(37) = 0.04$, $p = .484$, Cohen's $d = .01$. RTs in congruent trials did not differ between the painful and non-painful condition for either controls, $t(19) = 0.14$, $p = .444$, Cohen's $d = .06$, or patients, $t(18) = 0.56$, $p = .290$, Cohen's $d = .26$. Once again, there was no group difference in empathy, $t(37) = 0.46$, $p = .323$, Cohen's $d = .15$. Finally, RTs in incongruent trials did not differ between the painful and non-painful conditions for the controls, $t(19) = 0.72$, $p = .240$, Cohen's $d = .33$, whereas for patients, RTs in painful condition *differed* from those in the non-painful condition, $t(18) = 2.57$, $p = .010$, Cohen's $d = 1.21$. In contrast to healthy controls, patients' RTs were *faster* in incongruent trials under the painful condition compared with the non-painful condition, $t(37) = 2.05$, $p = .025$, Cohen's $d = .67$.

We also examined Stroop effects at baseline (non-painful) and during the empathy (painful vs. non-painful) conditions across groups. Figure 3 (left panel) displays effects of cognitive control at baseline condition. Patients and controls did not differ for Stroop facilitation (automatic processing), $t(37) = 0.93$, $p = .180$, Cohen's $d = .31$; or Stroop interference (controlled processing), $t(37) = 0.59$, $p = .279$, Cohen's $d = .19$. Thus Stroop interference and facilitation effects were similar between patients and controls, although patients performed generally worse on the task, which is consistent with Linden et al. [68]. To explore empathy effects on Stroop interference and facilitation between groups, we used comparative indices that contrasted differential responses in incongruent vs neutral and neutral vs congruent trials during empathically painful and non-painful conditions (Fig. 3, right panel).[3] A t test for the empathy effect on Stroop interference ($[Incongruent - Neutral]_{painful}$ vs. $[Incongruent - Neutral]_{Non\text{-}painful}$) approached significance, ($t(37) = 1.60$, $p = .059$, Cohen's $d = .53$), with a somewhat larger empathy effect on Stroop interference among patients (99.6 ms) compared with controls (44.6 ms). This suggests more improved execution function in patents with schizophrenia compared with controls. The empathy effect on Stroop facilitation ($[Neutral - Congruent]_{painful}$ vs.$[Neutral - Congruent]_{Non\text{-}painful}$) revealed no difference between patients (48.9 ms) and controls (37.7 ms), $t(37) = 0.43$, $p = .337$, Cohen's $d = .14$. Consistent with these outcomes, pairwise t tests for effects of empathy on interference and facilitation showed no difference for controls, $t(19) = 0.43$, $p = .336$, Cohen's $d = .20$, whereas among patients, the effect was larger for interference than for facilitation, $t(18) = 1.60$, $p = .063$, Cohen's $d = .75$.

Error rates

Figure 2 (bottom panels) depicts error rates for each group and condition. A 2 (Empathy: painful vs. non-painful) × 3 (Congruency: congruent, neutral, incongruent) × 2 (Group: patients vs. controls) repeated measures ANOVA revealed a main effect of Group, ($F(1,37) = 6.05$, $p = .019$, $\eta^2 = .14$), and a main effect of Congruency ($F(2,56) = 5.83$, $p = .009$, $\eta^2 = .17$). Patients made more errors compared with controls (patients: 7.0 %, SD = 0.06; controls: 3.9 %, SD = 0.06). The main effect of Congruency showed that for both groups, participants made more errors in incongruent trials, fewer errors in neutral trials, and the fewest errors in congruent trials. Empathy did not affect error rate, $F(1,37) = 0.11$, $p = .747$, $\eta^2 < .01$. No other significant effects were found.

Discussion

Previous studies demonstrated that schizophrenia is characterized by empathy deficits, which could be caused by dysfunction in a number of different cognitive domains [11, 43, 58, 65, 80]. However, none of these studies addressed how empathetic pain observation might affect cognition. Here, we used empathically painful stimuli to elicit empathy responses (cf., [37, 38, 50]) and probed how this affected automatic and controlled processing in schizophrenia. Our results demonstrate that compared with controls,

[3] The Stroop interference change was defined as the absolute values of the comparative index (see also Fig. 3 caption).

patients with schizophrenia show the following: (1) longer reaction times and higher error rates; (2) similar responding on neutral and congruent trials, with a larger empathy effect on incongruent trials; and (3) similar Stroop facilitation and interference in both non-painful and painful conditions, with a somewhat larger empathy effect on comparative Stroop interference index, as discussed further below.

Researchers have long debated the relative significance of a generalized versus specialized deficit in schizophrenia [26, 27, 36]. In contrast to previous work that suggested patients suffer from impaired controlled [20, 54, 55, 60, 64] or automatic processing [1, 3, 4, 13, 82, 105], we demonstrated that patients with schizophrenia show similar Stroop facilitation and interference compared with healthy controls in the non-empathetic condition. On the other hand, patients were slower and made more errors. It therefore appears that patients with schizophrenia do not suffer from specifically impaired automatic or controlled information processing as measured by the Stroop. This, perhaps, points toward a generalized impairment rather than a specialized deficit in schizophrenia [26, 27, 48, 108].

How do empathy and cognition interact in patients with schizophrenia? As we compare results from patients versus controls, it becomes apparent that the data fit well with the two-opposing effect model [47]. As Fig. 2 (left panel) shows, empathically painful compared with non-painful stimuli slowed RTs to neutral trials for controls, suggesting a general slowing, consistent with the resources theory which predicts that empathetic pain observation depletes central processing resources that are shared with cognition [30, 31, 84]. In addition, compared with the non-empathetic condition, controls exhibited unchanged RTs in congruent and incongruent trials during the empathetic condition. Empathetic pain processing may narrow attention to irrelevant information (i.e., word text) in incongruent trials and facilitate integration of congruent information (i.e., word and word color) in congruent trials. This empathy facilitation nullifies the basic slowing down effect, as disclosed in the neutral trials [14, 15, 29]. These data thus followed a two-opposing effect account—empathetic pain affects cognition through two different mechanisms: It slows performance in general and facilitates performance during incongruent and congruent trials in particular [49].

With regard to the patients with schizophrenia, they showed slower responses in neutral trials, unchanged RTs in congruent trials, and somewhat decreased RTs in incongruent trials for empathy (Fig. 2, right panel). Critically, empathetic pain processing led to similar improvement effects on Stroop facilitation and Stroop interference among those with Schizophrenia versus controls. These results thus are consistent with the two-opposing effect view described above, suggesting that empathy induced opposing effects, rather than a general impairment on cognition in schizophrenia. Moreover, the empathy effect on controlled processing was somewhat more pronounced in patients with schizophrenia than in controls (effect on Stroop interference: 99.6 vs. 44.6 ms). Considering that patients with schizophrenia suffer from impaired cognition, the finding that empathetic pain observation exerted similar effects in automatic processing and an even larger enhanced improvement in controlled processing in schizophrenia is very interesting, as it suggests that empathy not only compensates for the general slowing observed on neutral trials, but also attenuates attention to irrelevant information in incongruent trials more in patients than in controls.

What mechanism underlies the interaction of empathy on cognition? There is evidence that the frontoinsular (FI) and anterior cingulate cortex (ACC) are activated during empathetic pain processing [37, 38, 50]. It is possible that the empathy and cognition interaction leads to FI and ACC responses that in turn provide signals to the prefrontal cortex (PFC) and additional regions that enhance Stroop facilitation and interference in general. In essence, the notion that empathy (also emotion) relevant activation (e.g., in the FI, ACC) may interact with cognition directly reflects a common neuromodulatory phenomenon (e.g., coactivation and projections). Specifically, individuals with schizophrenia experience dysfunctional brain networks, for example, altered reciprocal connection between limbic and dorsal cortical structures [19, 32, 75, 98, 109]. We speculate that the upregulation of control in schizophrenia was due to the special activation of limbic structures [28, 53], which effectively link inputs with the dorsolateral PFC [16, 35, 78, 86]. For instance, it is reported that following recovery, patients with schizophrenia show increased activation in the PFC, and this activation is correlated with improved insight and social functioning [62]. Future studies that focus on dysfunctional brain networks underlying empathy deficits and studies using more experimental measures of empathy would be helpful toward unraveling the specific nature of the interaction between empathy and cognition in patients with schizophrenia.

To date, the general conclusion is that patients with schizophrenia have difficulties imagining another's feelings and taking on an appropriate emotional response to another's situation [12, 58, 63, 97]. In contrast, some researchers report very marginal empathetic deficits in schizophrenia [39, 97]. The present study was not designed to answer this question but might indicate that at least some components of empathetic pain processing are preserved in schizophrenia (for a similar opinion, see [68]), and empathy and cognition should be considered together.

One caveat in our study is that patients and controls were not matched perfectly in age, education, or gender, and we did not have a chance to measure intelligence. Therefore, it would be helpful for future studies to replicate our results,

controlling for these differences. However, we believe that these factors did not contribute significantly to results observed in the present study. The age difference between groups was not large, and no Stroop effect differences have been reported with such small age differences. Furthermore, neither of the groups had any problems performing this color-word Stroop task. If patients had general problems with the experiment, it would have affected both non-painful and painful tasks. The most important finding of our study was that compared with controls, patients showed similar increased Stroop facilitation and more decreased Stroop interference under the painful condition relative to non-painful condition.

Finally, our findings underscore the importance of considering the interaction of empathy and cognition in remediation programs. For example, we found that empathy improved execution function. Could the cognitive improvement be achieved in other empathetic contexts, or can it be extended to positive emotion or reward motivation conditions? Answering such questions could inform our understanding not only of empathy deficits, but also key targets for intervention in schizophrenia.

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Conflict of interest All authors declare that they have no conflicts of interest.

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