Psychiatry Research: Neuroimaging 271 (2018) 34–42

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Neural simulation mechanisms and social-emotional function in schizophrenia

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ARTICLE INFO

Keywords:
Mirror neurons
fMRI
Empathy
Social cognition
Mentalizing

ABSTRACT

Impairment in simulation, i.e., the generation of internal representations of experiences, may contribute to social dysfunction in schizophrenia spectrum disorders (SZ). Using a novel fMRI task, we identified neural representations generated during simulation of sensorimotor experiences and evaluated their associations with socioemotional function in 19 individuals with SZ and 24 psychiatrically-healthy controls (HC). Participants watched videos depicting a painful sensorimotor experience in the hand or foot of another person and were then asked to imagine how unpleasant it would be to undergo that experience themselves, eliciting simulation. A localizer task identified regions-of-interest (ROIs) within each participant's sensorimotor cortices (SC) recruited by firsthand sensory experiences in hands and feet. Simulation engaged these ROIs in HC and SZ. Simulation-related activation in ROIs did not differ between groups but was associated with participants' social function. Findings indicate that simulation elicits specific neural representations within the SC and the strength of these representations might be linked to social function.

1. . Introduction

Social impairment is a core feature of schizophrenia spectrum disorders (SZ), predicting conversion to psychosis (Cannon et al., 2008; Cornblatt et al., 2012), positive symptomatology (Collip et al., 2013), and functional disability (Mueser et al., 1991). However, social deficits are minimally responsive to standard schizophrenia treatments (Swartz et al., 2007). Investigating mechanisms that underlie social dysfunction is critical to developing targeted interventions to prevent and treat SZ.

Theory of Mind (ToM), the ability to understand and reason about others' mental states, is markedly impaired in SZ (Savla et al., 2013) and strongly predictive of social function (Brüne et al., 2007; Fett et al., 2011). Individuals with SZ demonstrate impairment in affective ToM, i.e., reasoning about others' emotional states (Shamay-Tsoory et al., 2007b), which may contribute to deficits in cognitive aspects of empathy, such as perspective-taking (Montag et al., 2007; Shamay-Tsoory et al., 2007a). Better understanding *how* these ToM deficits arise is critical to developing effective strategies for remediating social cognition and function in SZ (Kurtz and Richardson, 2012).

Simulation theory proposes that internal simulation is the primary mechanism by which people represent others' minds (Gallese et al., 2004). In this framework, an observer generates an internal representation of a target person's experience within the same brain regions that are recruited when processing that experience firsthand. This neural representation facilitates simulation, allowing the observer to imagine what she might think or feel in a similar situation, which, in turn, helps the observer understand the target's thoughts and feelings (Mitchell, 2009). For example, observing another person's actions in context (e.g., reaching to grasp a cup in order to drink water) can elicit simulation, facilitating understanding of that person's intentions; similarly, observing an emotional facial expression can engage simulation mechanisms, enabling understanding of another's affective state (Gallese, 2007; Gallese et al., 2004).

Neuroimaging studies indicate the presence of "mirror"-like neural mechanisms in a distributed network that includes the inferior frontal gyrus, premotor cortex, somatomotor cortex, and somatosensory-related cortices (Gazzola and Keysers, 2009; Rizzolatti and Fabbri-Destro, 2008). The sensorimotor cortices (SC) [including the somatomotor,

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https://doi.org/10.1016/j.pscychresns.2017.10.006
Received 2 May 2017; Received in revised form 12 September 2017; Accepted 22 October 2017
Available online 24 October 2017
0925-4927/

primary somatosensory, and secondary somatosensory cortices] may play an important role in representing affective experiences (Carr et al., 2003). The SC are engaged not only during firsthand emotional experience (Damasio et al., 2000) but also during emotion recognition (Adolphs et al., 2000), empathy (Bufalari et al., 2007), and prediction of affective responses (Hooker et al., 2008). Moreover, enhanced SC activation when reasoning about others' emotions is related to greater empathic accuracy (Zaki et al., 2009) and behavior (Hooker et al., 2008), suggesting that simulation mechanisms in the SC could facilitate social understanding.

Disruption of these neural simulation mechanisms may contribute to impaired empathy and social function in SZ. Therefore, recent studies have investigated simulation-related processes, such as imitation, in adults with SZ and psychiatrically-healthy controls (HC). Imitation, i.e., observing and reproducing others' actions, is thought to recruit simulation mechanisms to facilitate action representation (Park et al., 2008). Although behavioral imitation is impaired in SZ (Matthews et al., 2013; Park et al., 2008), it is unclear whether individuals with SZ show corresponding dysregulation of neural simulation mechanisms in the SC. For example, while a recent functional magnetic resonance imaging (fMRI) study indicated similar SC activation when imitating on-screen actions in HC and SZ (Horan et al., 2014), another demonstrated diminished specificity of SC activation to imitative actions in SZ (Thakkar et al., 2014). Yet another study revealed normative hemodynamic activation in SZ when observing others in pain but atypical SC activation specifically when instructed to switch between perspectives (i.e., imagining oneself versus others experiencing the pain) (Horan et al., 2016). This suggests specific disruption of neural mechanisms involved in imagining first- versus third-person experiences in SZ. Notably, these studies employed paradigms in which participants observed and/or imitated actions as they were depicted on-screen. Therefore, it is unclear whether individuals with SZ demonstrated an automatic, mirror-like neural response to observed external cues or engaged in simulation, i.e., generated an internal representation. Sophisticated interactions can necessitate deliberate use of simulation as a strategy to understand others' mental states and predict behavior. To characterize simulation deficits in SZ, research must test the ability to generate neural representations when attempting to imagine an experience *in the absence of external cues*.

In the current study, our first aim was to directly examine whether simulation elicits specific neural representations of salient sensorimotor experiences within the SC in SZ and HC. In the MRI scanner, participants watched a video depicting a person experiencing pain in a hand or foot. After the stimulus was removed from the screen, participants rated how unpleasant it would be to experience that pain themselves, eliciting simulation. An independent functional localizer task was used to identify SC activation elicited by firsthand sensorimotor experience in hands and feet. By leveraging the known somatotopic organization of the SC (Buccino et al., 2001), we defined functional regions-of-interest (ROIs) specifically involved in representing hand- and foot-related experiences for each participant. Utilizing these individually-tailored ROIs, we tested whether simulation elicited specific neural representations of sensorimotor experiences in SZ and HC. These methods allowed us to address our second aim: to compare the strength of these neural representations in SZ versus HC. Our final aim was to evaluate relations between the strength of neural representations and measures of empathy and broader social function. We predicted: (1) during simulation, HC and SZ would generate neural representations within specific regions of the SC involved in representing firsthand sensorimotor experiences; (2) SZ would show diminished strength of these neural representations relative to HC, indicating impaired simulation; and (3) the strength of these representations would be linked to individual variation in empathy and social function, implicating simulation as a core mechanism supporting social understanding and ability.

2. Methods

2.1. Participants

22 individuals with schizophrenia or schizoaffective disorder (SZ) and 26 psychiatrically-healthy controls (HC) were recruited from the greater Boston area. Inclusion criteria for all participants included: age 18–65, English-speaking, IQ > 70, no history of neurological or major medical illness, no history of head trauma, and no DSM-IV history of substance abuse or dependence within 6 months. SZ participants had a clinical diagnosis of schizophrenia or schizoaffective disorder, no comorbid DSM-IV axis I disorders, and no history of electroconvulsive therapy. HC participants had no lifetime axis I disorders or first-degree relatives with a psychotic disorder.

Participants completed the Structured Clinical Interview for DSM-IV Disorders (First et al., 2002) to screen for lifetime psychiatric diagnoses and the Wechsler Abbreviated Scales of Intelligence to assess IQ (Wechsler, 1999). SZ symptoms were assessed using an extended version of the Positive and Negative Syndrome Scale (PANSS-E) (Kay et al., 1987; Poole et al., 2000). Participants' role functioning (e.g., performance in school, work, or home) was assessed using the Global Functioning: Role Scale (GF-Role) (Cornblatt et al., 2007). Data from 5 participants were excluded from analysis due to poor quality (see Section 2.3.1), yielding a final sample of 19 SZ and 24 HC individuals. HC and SZ groups did not differ in demographics or IQ (Table 1). Participants provided written informed consent in accordance with the Institutional Review Board at Harvard University and were compensated for participation.

2.2. Experimental procedure

2.2.1. Measures of social function

The Interpersonal Reactivity Index, a 28-item self-report measure, was used to evaluate multiple facets of empathy (Davis, 1980, 1983). We were interested in two subscales: perspective-taking (IRI-PT), which assesses the tendency to adopt others' points-of-view (e.g., "When I'm upset at someone, I try to put myself in his shoes for a while") and empathic concern (IRI-EC), which measures concern and sympathy for others (e.g., "I often have tender, concerned feelings for people less fortunate than me"). Each subscale included 7 items rated from 0 ("does not describe me very well") to 4 ("describes me very well").

The Social Adjustment Scale Self-Report (SAS-SR), a 54-item self-report questionnaire, assessed current function in six domains: work, social and leisure activities, relationships with extended family, marital role, parental role, and role within the family unit (Weissman et al., 1978). Raw SAS-SR scores were averaged across domains and converted to a gender-adjusted *T* score indexing overall social impairment.

The Global Functioning: Social Scale (GF-Social), an interview-based measure, assessed quantity and quality of relationships, peer conflict, and family involvement on a scale from 1 ("extreme dysfunction") to 10 ("superior function") (Cornblatt et al., 2007).

2.2.2. Simulation fMRI task

In the MRI scanner, participants performed a novel task designed to elicit simulation (Fig. 1) (Lincoln et al., 2010, 2017). During experimental trials, participants observed a video depicting a person experiencing accidental pain in either a (a) hand (e.g., hitting a hand with a hammer) or (b) foot (e.g., shutting a foot in a door). Stimuli included different types of sensory experience (pressure, mechanical, and thermal). After the video was removed from the screen, participants were instructed to rate how unpleasant it would be for them to have that experience (e.g., "How unpleasant would it be for you to be cut by a knife?") on a scale from 1 ("not at all unpleasant") to 5 ("extremely unpleasant"), prompting them to generate an internal representation of the sensorimotor experience in order to judge how it might feel.

Table 1
Participant demographics and behavioral data.

	SZ	HC	Group differences
N	19	24	
Gender (male/female)	10/9	18/6	$\chi^2(1, N = 43) = 1.45, p = 0.23$
Age	38.10 (9.56) [21–58]	35.38 (11.37) [20–53]	$t(41) = -0.86, p = 0.40, d = 0.26$
Education (years)	14.53 (2.25) [10–18]	14 (2.70) [11–21]	$t(41) = -0.70, p = 0.49, d = 0.21$
Race/ethnicity (*N*)			$\chi^2(5, N = 43) = 5.35, p = 0.37$
White or Caucasian	9	17	
Black or African American	6	4	
Hispanic or Latinx	1	1	
Asian or Asian American	2	0	
Hawaiian or Pacific Islander	0	1	
Multiracial	1	1	
IQ[a]	106.95 (14.37) [82–133]	108.58 (10.39) [88–127]	$t(32) = 0.42, p = 0.68, d = 0.13$
GF – Role	5.58 (1.80) [3–8]	8.08 (1.21) [6–10]	$t(30) = 5.19, p < 0.001, d = 1.67$*
Diagnosis (n)			
Schizophrenia	15		
Schizoaffective	4		
PANSS-E symptoms			
Negative symptoms	13.05 (5.47) [7–27]		
Positive symptoms	16.37 (5.74) [8–30]		
Disorganized symptoms	7.68 (4.00) [5–18]		
Duration of illness (years)[b]	16.66 (11.83) [2–42]		
CPZ equivalent	350.88 (314.59) [0–1000]		
Social variables			
IRI-PT	30.70 (4.32) [20–37]	32.46 (4.32) [27–42]	$t(39) = 1.33, p = 0.19, d = 0.41$
IRI-EC	31.95 (5.55) [21–42]	31.75 (4.29) [24–42]	$t(33) = -0.13, p = 0.90, d = 0.04$
SAS-SR	67.47 (16.48) [43–97]	51.46 (10.15) [36–76]	$t(28) = -3.71, p < 0.001, d = 1.17$*
GF – Social[c]	6.11 (1.52) [3–9]	8.56 (1.34) [6–10]	$t(36) = 5.49, p < 0.001, d = 1.72$*
Simulation task			
Unpleasantness rating (Hand)[d]	3.69 (0.69) [2.07–4.62]	3.77 (0.65) [2.34–4.90]	$t(35) = 0.39, p = 0.70, d = 0.12$
Unpleasantness rating (Foot)[d]	3.71 (0.62) [2.07–4.72]	3.84 (0.60) [2.83–4.97]	$t(34) = 0.64, p = 0.53, d = 0.20$
Control rating[d]	3.30 (0.61) [2.00–4.40]	3.25 (0.56) [2.25–4.57]	$t(33) = -0.28, p = 0.78, d = 0.09$

Notes. All data are presented as mean, (SD), [range] unless otherwise noted. Welch's *t*-tests were used to test group differences; adjusted degrees of freedom were rounded to the nearest integer.

[a] Full-scale IQ scores were estimated using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI).

[b] Data were not collected from one SZ participant.

[c] Data were not collected from one HC participant.

[d] Due to technical error at the scanner, ratings were not collected from one SZ participant.

* Group differences were significant at $p < 0.05$.

During control trials, participants observed a static video depicting an object from the experimental condition (e.g., the hammer that hit a hand in an experimental stimulus was presented alone in the matched control stimulus). Participants were then instructed to rate the relative size of the object (e.g., “How much bigger is that peeler than a stop sign?”) on a scale from 1 (“much smaller”) to 5 (“much bigger"), prompting them to imagine the objects in order to evaluate size. This condition allowed us to control for activation associated with object representation when evaluating neural representations of sensorimotor experiences. The task yielded six conditions: (1) observation of hand pain (Hand Observation), (2) observation of foot pain (Foot Observation), (3) observation of control object (Control Observation), (4) simulation of hand pain (Hand Simulation), (5) simulation of foot pain (Foot Simulation), and (6) object size representation (Control Question).

During the task, participants viewed 32 trials depicting hand pain, 32 trials depicting foot pain, and 32 trials depicting control stimuli. Trials consisted of a video stimulus (4 s), a fixation cross (4, 6, or 8 s jittered), a question screen (4 s), and another fixation cross (4, 6, or 8 s jittered). Participants responded to questions using a five-button

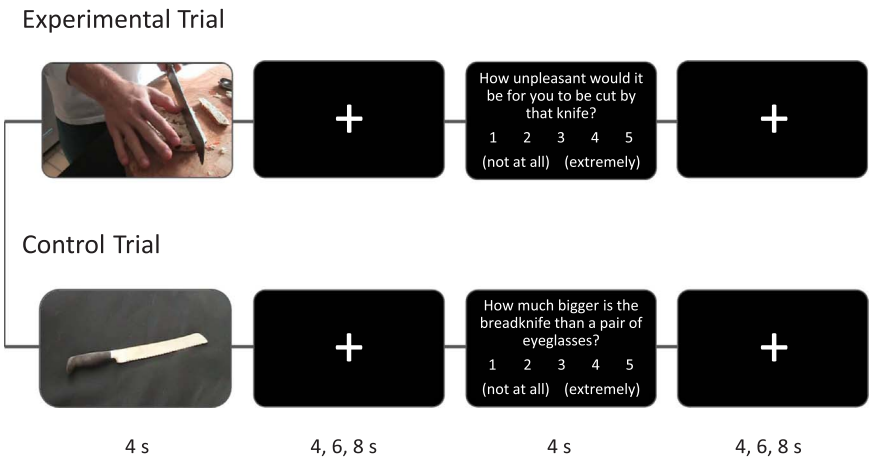

Fig. 1. Simulation task. In the experimental trial example, participants observed a person accidentally cutting his finger with a bread knife, followed by a jittered fixation cross, a question screen asking them to rate how unpleasant it would be for *them* to be cut by the knife, and then another fixation cross. In the control trial example, participants observed the static bread knife presented alone, followed by a jittered fixation cross, a question screen asking them to rate the size of this object relative to another, and then another fixation cross. Participants logged responses to the question screens via button-press for both trial types.

response pad. Trials were presented in fixed, pseudorandomized order using E-Prime and Matlab software.

2.2.3. Localizer task

Participants also completed one functional run of an independent localizer task, which required participants to rub their hands or feet together or move their mouths. The single run of this task included five 20 s blocks of movement for Hand Motion, Foot Motion, and Mouth Motion, with 12 s rest periods. Mouth Motion was not a condition of interest in the current analyses. This task identified neural activation associated with firsthand sensorimotor experiences in each participant's hands and feet.

2.3. fMRI acquisition and analysis

fMRI data were collected on a 3 T Siemens Tim Trio scanner at Harvard University's Center for Brain Science with echoplanar images (40 oblique-axial slices; 3 × 3 × 3 mm isotropic voxels; TE = 30 ms; TR = 2560 ms, flip angle = 85 degrees). A T1-weighted anatomical image was acquired with an MPRAGE sequence (176 axial slices, 1 × 1 × 1 mm voxels). Data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) within the general linear model (GLM) framework. The first four volumes of functional runs were discarded prior to analysis to ensure steady-state magnetization. Preprocessing included realignment to the mean functional image, co-registration to the anatomical image, normalization to MNI template space, and smoothing with an 8 mm Gaussian kernel. Data were high-pass filtered at 128 ms.

2.3.1. Simulation task analysis

Within each subject, hemodynamic response to each observation condition (Hand Observation, Foot Observation, and Control Observation) was modeled at the onset of the video and to each simulation condition (Hand Simulation, Foot Simulation, and Control Question) at the onset of the question screen with a duration of 4 s. Contrast files were generated for Hand Observation > Control Observation, Foot Observation > Control Observation, Hand Simulation > Control Question, and Foot Simulation > Control Question.

The Artifact Detection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) was used to identify outlier scans in global signal (> ± 4 *SD*) and movement (> 3 mm from the previous volume), which were entered into the GLM as nuisance regressors (Yin et al., 2015). The number of outliers did not differ between HC and SZ (Mann-Whitney *U*-test: $U = 240$, $p = 0.77$). Participants with greater than 4% of functional scans identified as outliers were excluded from analyses. Additionally, data from one SZ participant was excluded due to ghosting artifact. In total, data from 2 HC and 3 SZ participants were excluded from analysis due to poor quality.

2.3.2. Whole brain ANOVA

To verify expected task-related activation, a full-factorial ANOVA was conducted to examine the main effects of observation (Hand Observation > Control Observation; Foot Observation > Control Observation) and simulation (Hand Simulation > Control Question; Foot Simulation > Control Question) relative to control conditions. Following-up on our ROI analyses (described in Section 2.3.4.), we also examined between-group differences at the whole brain-level. This allowed us to confirm differential recruitment (HC > SZ; SZ > HC) of other neural mechanisms beyond our ROIs during simulation versus control conditions. Whole-brain results are reported at a peak threshold of $p < 0.0001$, family-wise error (FWE) corrected to $p < 0.05$ at the cluster level.

2.3.3. Localizer task analysis

In the localizer task, hemodynamic response to the three movement conditions (Hand, Foot, and Mouth Motion) was modeled at the onset of each 20 s movement block. Contrasts files were created for Hand Motion > Foot Motion and Foot Motion > Hand Motion. ART was used to identify outlier scans [global signal (> ± 4 *SD*) or head movement (> 3 mm composite motion)], which were entered into the GLM as nuisance regressors. This allowed us to account for variance associated with motion in our model, maximizing sensitivity to task-related activity. Task-motion correlation plots were visualized for linear and rotational motion parameters and inspected to verify minimal association. The number of motion outliers did not differ between HC and SZ (Mann-Whitney *U*-test: $U = 248$, $p = 0.62$).

2.3.4. ROI definition and analyses: Evaluating neural representations in the SC

Primary analyses focused on simulation-related activity within *a priori* ROIs, i.e., the areas of each participant's SC activated by the firsthand sensorimotor experience in hands and feet during the localizer task. The somatotopic organization of the SC guided the definition of hand and foot ROIs (Buccino et al., 2001; Stippich et al., 2002). For each participant, we defined hand ROIs as 8 mm spheres centered at the positive maxima for Hand Motion > Foot Motion located nearest to the 'hand knob' on the precentral gyrus (Stippich et al., 2002; Yousry et al., 1997) and foot ROIs as 3 mm spheres centered at the positive maxima for Foot Motion > Hand Motion located nearest to the intersection of the central sulcus and longitudinal fissure (Stippich et al., 2002) in each hemisphere. Maxima were identified for each contrast at $p < 0.001$, $k > 10$, uncorrected. If activation within the SC was not identifiable at $p < 0.001$, the threshold was raised iteratively ($p < 0.01$, then $p < 0.1$) until local maxima were observable (Bedny et al., 2012). Six SZ and two HC participants required this p threshold adjustment to identify local maxima. Our procedure yielded four ROIs in the SC (Right and Left Hemisphere Hand ROIs; Right and Left Hemisphere Foot ROIs) for each participant. Average MNI coordinates are reported for HC and SZ in Fig. 3.

Given our specific interest in simulation-related neural representations, ROI analyses focused on simulation conditions. Contrast estimates were extracted for Hand Simulation > baseline from each Hand ROI and for Foot Simulation > baseline from each foot ROI. Contrast estimates for Hand Simulation > Control Question and Foot Simulation > Control Question were also computed. Distribution of neural data was inspected for normality.

To confirm that our simulation manipulation elicited neural representations of hand- and foot-related sensorimotor experiences within the SC, we examined whether ROIs demonstrated significantly greater activation to Hand Simulation and Foot Simulation relative to Control Question. In addition, we evaluated whether SZ individuals demonstrated atypical neural activation to simulation within ROIs. Therefore, we conducted a repeated measures ANOVA with task (Simulation > baseline and Control > baseline) and ROI (Right Hemisphere Hand, Left Hemisphere Hand, Right Hemisphere Foot, and Left Hemisphere Foot) as within-subjects factors and group (HC, SZ) as the between-subjects factor. Planned simple effect tests were carried out for significant interaction terms using a statistical threshold of $p < 0.05$ (two-sided).

2.4. Brain-behavior associations

Separate regression models tested associations between the strength of simulation-related neural activity in ROIs and each social measure (IRI-PT, IRI-EC, SAS-SR, and GF-Social) across HC and SZ. To test the unique effect of activity in a given ROI on social function for HC and SZ, initial regression models included ROI activity, diagnostic group, and the interaction term as predictors and the social measure as the dependent variable. We did not predict differential relations between ROI activity and social function in SZ versus HC; non-significant interaction terms were dropped, and final models were run with only ROI activity

and group as predictors. Predictors were checked for multicollinearity. Model residuals were inspected to confirm normality and homoscedacity. 95% confidence intervals (CIs) were derived through bias-corrected and accelerated (BCa) bootstrapping from 1000 samples. We used the adaptive Benjamini–Hochberg correction (Benjamini and Hochberg, 2000), which controls the false-discovery rate, to evaluate whether brain-behavior associations remained significant ($p < 0.05$) after multiple comparison correction (i.e., eight tests conducted).

3. Results

3.1. Behavioral results

Table 1 summarizes behavioral results. SZ participants demonstrated greater social maladjustment (SAS-SR *T* scores) and poorer global social function (GF-S) but did not differ significantly from HC in empathic perspective-taking (IRI-PT) or concern (IRI-EC). Importantly, HC and SZ groups did not differ in ratings of how unpleasant it would be to experience the pain depicted in the task, confirming similar subjective experience of imagined pain.

3.2. Whole brain ANOVA

Main effects for observation and simulation conditions are reported for the full sample (Table 2, Fig. 2). Expected task-related activation was observed: both SZ and HC participants demonstrated activation in SC regions (including somatomotor and somatosensory cortices) when observing and simulating hand- and foot-related sensorimotor experiences. Midline cortical structures, i.e., the posterior cingulate cortex, precuneus, and medial prefrontal cortex, also demonstrated activation during hand and foot simulation. In addition, whole-brain results indicated no significant differences in activation between HC and SZ.

3.3. ROI analysis: Evaluating neural representations in the SC

Repeated measures ANOVA with a Greenhouse-Geisser correction revealed a significant interaction between ROI and Task [$F(1.87, 76.64) = 25.66$, $p < 0.001$, $\eta^2_{partial} = 0.385$], as well as significant main effects of ROI [$F(1.58, 64.86) = 46.82$, $p < 0.001$, $\eta^2_{partial} = 0.533$] and Task [$F(1.00, 41.00) = 6.60$, $p = 0.014$, $\eta^2_{partial} = 0.139$]. Importantly, the main effect of group and all interactions with group were non-significant [all Fs < 0.70, all ps > 0.48].

Planned simple effects tests of the significant interaction (ROI by Task) revealed greater activation to Hand Simulation versus Control Question in the Right Hemisphere Hand ROI [$t(42) = 2.97$, $p = 0.005$, $d = 0.45$] and to Foot Simulation versus Control Question in both Right [$t(42) = 6.59$, $p < 0.001$, $d = 1.00$] and Left Hemisphere Foot ROIs [$t(42) = 4.85$, $p < 0.001$, $d = 0.74$] across groups. The Left Hemisphere Hand ROI demonstrated reduced activation to Hand Simulation versus Control Question [$t(42) = -3.24$, $p = 0.002$, $d = -0.50$]. Contrast estimates for Hand Simulation > Control Question in each Hand ROI and for Foot Simulation > Control Question in each Foot ROI are depicted in Fig. 3 for HC and SZ. Since the Left Hemisphere Hand ROI was not engaged during simulation, it was dropped from subsequent brain-behavior analyses. Given the strong correlation between Right and Left Foot ROI activity ($r = 0.65$, 95% CI [0.29, 0.82], $p < 0.001$), we collapsed Foot ROI data across hemispheres and used the resulting Bilateral Foot ROI for subsequent analyses.

3.4. Brain-behavior associations

Results of multiple regression models are reported in Table 3. Neural activity in the Bilateral Foot ROI demonstrated a significant unique association with GF-S scores: stronger neural representations were associated with better social function, above and beyond the effect of group. However, this relationship did not survive multiple comparison correction. Simulation-related ROI activity did not uniquely predict SAS-SR, IRI-PT, or IRI-EC scores.

4. Discussion

Using a novel fMRI paradigm, the current study evaluated neural mechanisms supporting sensorimotor simulation in SZ and HC. SZ and HC participants did not differ in behavioral ratings of how unpleasant it would be to experience the pain depicted, confirming similar subjective experience of imagined pain. Whole-brain analyses revealed expected task-related activation in the SC across SZ and HC, verifying that our simulation task recruited this aspect of the mirror neuron system. These findings build upon prior studies of social cognitive processes, including emotion recognition (Adolphs et al., 2000), social signal perception (Hooker et al., 2010), and empathy (Bufalari et al., 2007; Zaki et al., 2009), which have implicated the SC in embodied simulation. Our whole-brain analyses revealed that simulation recruited some nodes of the mirror neuron network (e.g., the posterior superior temporal gyrus, middle temporal gyrus, and SC) but not others (e.g, inferior frontal gyrus) engaged by action observation and/or imitation in previous studies (Caspers et al., 2010; Iacoboni and Dapretto, 2006). This highlights the need to evaluate neural correlates of simulation in the absence versus presence of external cues. Notably, we found that simulation elicited activation in the medial prefrontal cortex and posterior cingulate cortex, key nodes of a network associated with self-reflective cognitive processes, such as simulating one's own future experiences (Buckner and Carroll, 2007). Given previous findings of midline cortical structure dysregulation in SZ (Harrison et al., 2007; Holt et al., 2011), further studies should evaluate contributions of these regions to simulation and social function in SZ.

Our novel methodology allowed us to address three primary questions about simulation. First, we tested whether SZ and HC individuals generate specific neural representations of sensorimotor experiences in the SC during simulation. Across diagnostic groups, participants engaged the Right Hemisphere Hand ROI and Bilateral Foot ROI when simulating the experiences observed in others' hands and feet, respectively. This suggests that individuals generate an internal representation of imagined sensorimotor experiences within the *same regions* of the SC in which they represent firsthand experiences, providing a parsimonious mechanism for internal representation of sensations and associated affective responses. Interestingly, the Left Hemisphere Hand ROI showed deactivation during simulation relative to the control condition. This finding is difficult to clearly interpret, as activity in this ROI might reflect not only neural simulation mechanisms but also those involved in preparing or executing small movements with right hand (e.g., getting ready to log a response or fidgeting). Another study employing our experimental procedure also did not find simulation-related activation in the Left Hemisphere Hand ROI, indicating lack of engagement across samples (Lincoln et al., 2010, 2017). Nevertheless, our findings in the Right Hemisphere Hand and Bilateral Foot ROIs provide evidence that individuals generate neural representations within the SC to imagine what it would feel like to experience pain they observed in another person, consistent with simulation accounts of social cognition (Gallese et al., 2004).

Second, to test possible impairment of simulation mechanisms in SZ, we compared the strength of sensorimotor representations in SZ and HC. Simulation-related activation in ROIs did not differ significantly between groups; individuals with SZ demonstrated comparable strength of representations in the SC relative to HC. Importantly, the SC constitute only one node of the distributed networks implicated in simulation. It is possible that other regions of the mirror neuron network (e.g., inferior frontal gyrus) or areas that support self-reflective thinking (e.g., the medial prefrontal cortex) might show dysregulation during simulation in SZ. However, our whole-brain analyses suggest no significant difference between SZ and HC in engagement of broader neural mechanisms during simulation. Results are consistent with previous

Table 2
Whole-brain analysis (ANOVA): main effects of condition across HC and SZ.

	Region	BA	Cluster size	MNI coordinates x y z	Peak voxel *t*-value
Hand Observation > Control Observation	Middle temporal gyrus/Inferior parietal lobule/Postcentral gyrus (R)	39/2/5	2479	51 −64 4	15.73
	Inferior parietal lobule/ Postcentral gyrus (L)	40/1/2	2293	−57 −28 25	15.34
	Inferior frontal gyrus/Precentral gyrus (L)	44/9	1302	−51 8 16	11.44
	Inferior frontal gyrus/Precentral gyrus (R)	44/9	1912	51 14 10	10.83
	Precentral gyrus/Superior frontal gyrus (L)	6	325	−27 −7 55	9.05
	Fusiform gyrus (L)	37	75	−42 −46 −20	8.99
	Cingulate gyrus (L)	31	49	−12 −25 40	8.28
	Cerebellum (R)	–	50	15 −73 −44	7.90
	Supplementary motor area (Bilateral)	6	385	9 17 61	7.54
	Lingual gyrus (Bilateral)	18	856	6 −79 −5	7.40
	Cingulate gyrus (Bilateral)	24	115	−3 −1 37	7.40
	Thalamus (R)	–	154	18 −28 4	7.09
	Thalamus (L)	–	178	−9 −19 10	7.03
	Cerebellum (L)	–	51	−9 −76 −44	6.77
	Superior occipital lobe/Cuneus (R)	19	93	27 −79 37	6.15
	Cingulate gyrus (R)	31	24	12 −22 40	6.02
	Putamen (R)	–	33	21 2 7	5.57
Foot Observation > Control Observation	Inferior parietal lobule/Postcentral gyrus (L)	40/2	1328	−57 −28 25	16.42
	Middle temporal gyrus/Middle occipital gyrus (R)	39/37	1983	48 −64 4	14.55
	Middle temporal gyrus/Middle occipital gyrus (L)	39/19	684	−48 −67 7	14.02
	Inferior frontal gyrus/Precentral gyrus (L)	44/45	817	−54 8 19	11.41
	Inferior frontal gyrus/Precentral gyrus (R)	44/45	1219	51 14 10	10.03
	Fusiform gyrus (L)	37	76	−42 −46 −20	8.79
	Cingulate gyrus (L)	31	37	−12 −25 40	8.34
	Cerebellum (R)	–	42	15 −73 −44	7.56
	Superior frontal gyrus/Precentral gyrus (L)	6	256	−24 −7 58	7.50
	Cingulate gyrus (Bilateral)	24	66	−3 −1 37	7.35
	Thalamus (L)	–	93	−15 −25 7	6.38
	Lingual gyrus (R)	18	193	6 −79 −5	6.24
	Thalamus (R)	–	67	18 −28 4	6.17
	Cerebellum (R)	–	22	24 −67 −23	5.82
	Cerebellum (L)	–	39	−21 −67 −50	5.76
	Supplementary motor area (R)	6	93	6 17 58	5.66
	Insula (L)	47	36	−27 17 −14	5.19
	Middle frontal gyrus (L)	46	86	−48 44 19	5.18
	Superior occipital lobe (R)	19	36	27 −82 37	5.10
	Superior occipital lobe (L)	19	36	−24 −82 28	4.83
	Superior medial frontal gyrus (R)	8	20	6 44 43	4.79
Hand Simulation > Control Question	Medial frontal gyrus/ Cingulate gyrus/ Precuneus (Bilateral)	10	5038	−6 56 −2	9.67
	Cerebellum (L)	–	96	−30 −82 −35	6.91
	Paracentral Lobule/ Postcentral gyrus/ Precentral gyrus (Bilateral)	4/5/6	560	−6 −28 64	6.42
	Cerebellum (R)	–	27	30 −82 −35	6.21
	Putamen/Amygdala (R)	–	37	27 −7 −8	5.58
Foot Simulation > Control Question	Posterior cingulate cortex/ Precuneus/ Superior temporal gyrus/ Supramarginal gyrus (Bilateral)	31	6632	−33 −52 4	10.20
	Cerebellum (R)	–	47	30 −79 −35	7.27
	Cerebellum (L)	–	86	−30 −79 −35	6.91
	Paracentral lobule (Bilateral)/ Postcentral gyrus (R)/Precentral gyrus (R)	6/3/4	791	−3 −28 61	6.72
	Posterior superior temporal gyrus (R)	22	33	57 −58 16	4.74

Notes. Regions demonstrating significant neural activity for the main effects of condition are reported at a peak threshold of $p < 0.0001$, corrected at the cluster-level to $p < 0.05$.

studies investigating imitation and empathy (Horan et al., 2014, 2016), which indicate broadly similar patterns of neural activation in SZ and HC. By employing a novel paradigm eliciting simulation in the absence of external cues, the current study suggests that neural simulation mechanisms in the SC may not be impaired in SZ.

Third, we tested whether the strength of neural representations generated during simulation was linked to social function. Simulation-related activation in the Bilateral Foot ROI predicted better interviewer-rated social function; however, this relationship did not survive correction for multiple comparisons and should therefore be interpreted with caution. Findings suggest that robust internal representations of salient sensorimotor experiences *might* support social function, in line with simulation accounts of social understanding (Gallese et al., 2004). Reduced strength of these neural representations may reflect difficulties in simulation, contributing to marked social dysfunction in SZ and more subtle social difficulties in psychiatrically-healthy individuals. The strength of hand- or foot-related experiences in the SC were not linked to self-evaluated empathic tendencies or social adjustment, possibly because these self-report measures rely upon higher-order inferential processes requiring insight. Further work is needed to clarify relations between neural simulation mechanisms and socioemotional function in SZ and HC.

Interestingly, neural representations of foot- but not hand-related experiences were associated with social function. Our ROI analyses focused on representations within the specific regions of the SC recruited by firsthand experience. Given the larger expanse of cortical surface that supports representation of hands versus feet (Disbrow et al., 2000), our Hand ROIs may not have captured the full extent of

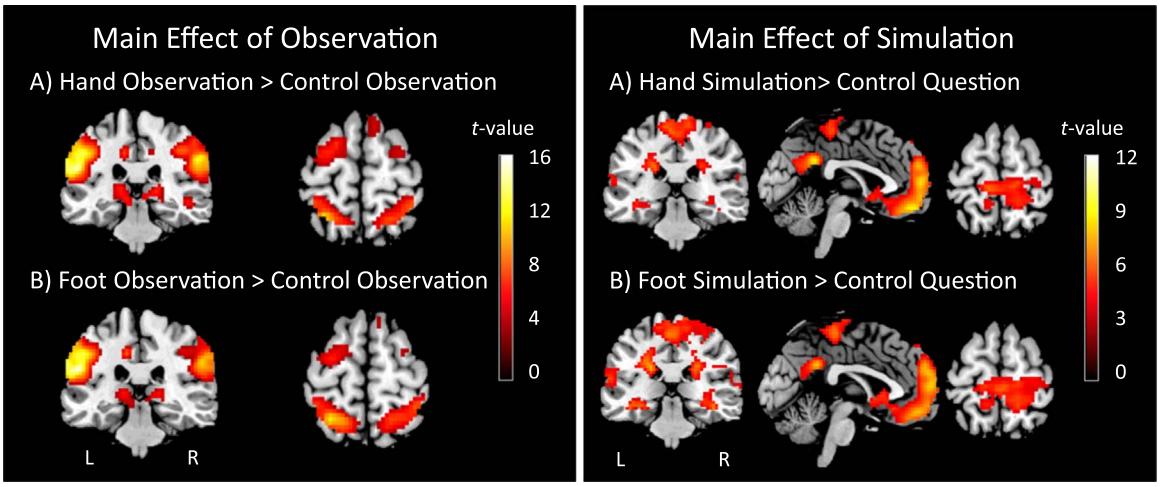

Fig. 2. Whole brain analysis: task verification. A) Top panel depicts the positive main effects of Hand Observation > Control Question and Hand Simulation > Control Question in a full-factorial ANOVA. B) Bottom panel depicts the positive main effects of Foot Observation > Control Observation and Foot Simulation > Control Question in a full-factorial ANOVA. All images are displayed at $p < 0.0001$, corrected at the cluster-level to $p < 0.05$. Slices are shown at MNI coordinates [−1 −29 67].

variation in SC activity during hand simulation. Prior research suggests that imagining hand movements recruits unique aspects of the SC compared to executing the same movement, although these neural representations partly overlap (Stippich et al., 2002). Future work should test whether imagining hand experiences is supported, in part, by aspects of the SC that are not strongly engaged by direct experience.

We note that our experimental task elicited representations of how unpleasant it would be for *oneself* to experience the observed pain. Simulation theory proposes that these self-referential representations are then used to make social inferences. However, this study did not test the translation of these representations to understand others' experiences. Individuals with SZ could demonstrate atypical neural activation at this critical step for social cognition, contributing to impairment in social understanding. Also, because the paradigm evaluated simulation of painful sensorimotor experiences, it remains unclear whether simulation elicits representations of positive experiences or other negative experiences in the SC. Although the SC has been implicated in reasoning about others' positive and negative emotional responses (Hooker et al., 2008; Zaki et al., 2009), this hypothesis remains to be directly evaluated. Moreover, simulation of other salient affective experiences (e.g., social rejection) could be impaired in SZ, contributing to social dysfunction.

Findings should be interpreted in light of key limitations. The modest sample size may have limited our power to detect group differences in activation and elucidate brain-behavior relations. Additionally, our procedure for defining individualized ROIs may have impacted findings: increasing the p threshold to identify local peak activations in the SC during hand and foot movement may have led to definition of ROIs based on weaker signal in some participants. It is also possible that psychoactive medication use affected neural activity and current social function in SZ. These limitations should be addressed by future studies.

The current work adds to the literature supporting simulation accounts of interpersonal understanding (Gallese et al., 2004). Findings reveal that individuals generate neural representations of observed sensorimotor experiences in the SC during simulation and that the strength of these representations might be linked to individual variation in social function. However, future research is needed to confirm this brain-behavior relationship. Given evidence of the neuroplasticity of the SC in human adults (Feldman and Brecht, 2005; Yang et al., 1994), neural representations in this region may hold promise as targets for future social-cognitive interventions in SZ and other disorders characterized by social deficits, such as autism.

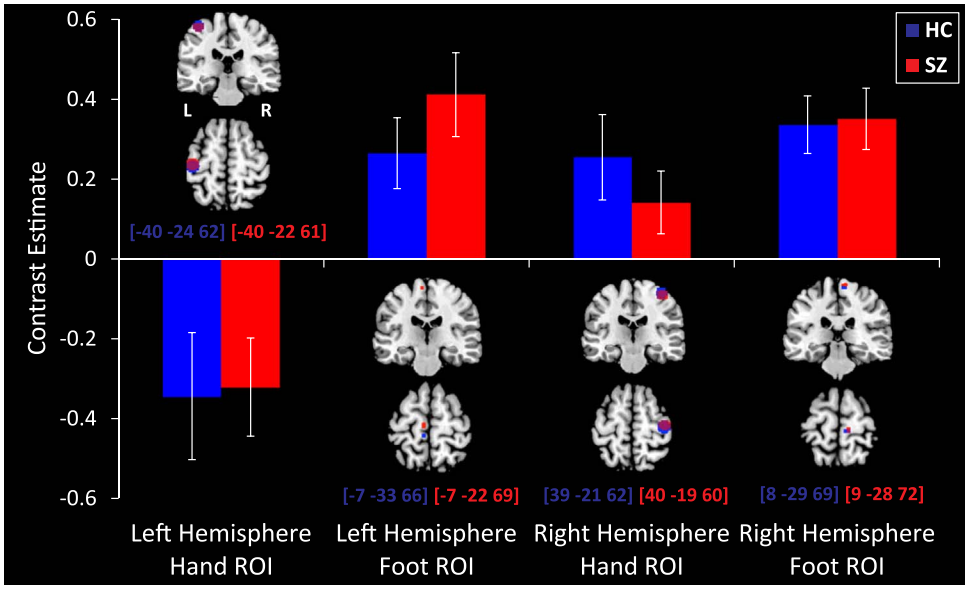

Fig. 3. Region of interest (ROI) data. Mean contrast estimates for HC and SZ are plotted for the Left and Right Hemisphere Hand and Foot ROIs. Error bars represent the standard error of the mean. Because ROIs were individually-tailored for each participant, MNI coordinates averaged across participants are reported in square brackets for HC (blue) and SZ (red). The blue and red spheres represent the average regions from which contrast estimates were extracted for HC and SZ, respectively.

Table 3
Brain-behavior associations: Multiple regression models predicting social measures.

		Parameter Estimates & Significance		Model Fit	
		b [95% CI]	*p*	*F*(2,40)	R^2 [95% CI]
Neural Activity + Group → IRI-PT					
Right Hand ROI	Activity	0.79 [−1.53, 3.54]	0.604	1.00	0.05 [0.00, 0.18]
	Group	−1.68 [−4.45, 0.86]	0.222		
Bilateral Foot ROI	Activity	1.78 [−2.13, 5.21]	0.352	1.32	0.06 [0.00, 0.19]
	Group	−1.92 [−4.69, 0.71]	0.162		
Neural Activity + Group → IRI-EC					
Right Hand ROI	Activity	0.90 [−2.08, 4.38]	0.601	0.15	0.01 [0.00, 0.02]
	Group	0.30 [−3.14, 3.37]	0.846		
Bilateral Foot ROI	Activity	1.44 [−1.92, 6.81]	0.502	0.24	0.01 [0.00, 0.05]
	Group	0.08 [−3.21, 3.11]	0.958		
Neural Activity + Group → SAS-SR					
Right Hand ROI	Activity	−1.56 [−11.67, 6.76]	0.805	7.54	0.27 [0.07, 0.47]
	Group	15.89 [7.81, 25.03]	< 0.001*		
Bilateral Foot ROI	Activity	−6.29 [−19.73, 4.67]	0.281	8.31	0.29 [0.08, 0.49]
	Group	16.52 [8.31, 25.07]	< 0.001*		
Neural Activity + Group → GF-Social*					
Right Hand ROI	Activity	0.35 [−0.46, 1.67]	0.513	15.46	0.44 [0.18, 0.63]
	Group	−2.44 [−3.25, −1.58]	< 0.001*		
Bilateral Foot ROI	Activity	1.51 [0.45, 2.52]	0.013*,†	21.16	0.52 [0.23,0.67]
	Group	−2.58 [−3.41, −1.76]	< 0.001*		

Notes. Parameter estimates (*b*) and significance (*p*), as well as model fit (*F* statistic and R^2) are reported for each multiple regression model run.
* GF-Social data were not collected for one participant, affecting degrees of freedom [*F*(2,39)].
* Significant at $p < 0.05$.
† Does not remain significant after controlling the false-discovery rate.

Acknowledgements

This work was supported by the RAND Fund, Harvard University (C.I.H.); the Sackler Scholar Programme in Psychobiology (L.M.T., S.H.L.); the Frank Knox Memorial Scholarship (L.M.T.); and the Karen Stone Fellowship (C.E.M). The authors thank Dr. Hong Yin, Emily Carol, Steven Felix, and Erik Nook for their practical and conceptual contributions.

Conflicts of interest

The authors declared that they had no conflicts of interest with respect to authorship or the publication of this article.

Contributors

S.H.L. and C.I.H. developed the study concept. S.H.L., C.I.H., L.M.T., and D.D.F. contributed to study design and data collection. C.E.M. and C.I.H. conducted data processing, analysis, and interpretation of results. C.E.M. drafted the manuscript. All authors provided feedback on the manuscript and approved submission of the final version.

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