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Tool-use Extends Peripersonal Space Boundaries in Schizophrenic Patients

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Background and Hypothesis: **A primary disruption of the bodily self is considered a core feature of schizophrenia (SCZ). The "disembodied" self might be underpinned by inefficient body-related multisensory integration processes, normally occurring in the peripersonal space (PPS), a plastic sector of space surrounding the body whose extent is altered in SCZ. Although PPS is a malleable interface marking the perceptual border between self and others, no study has addressed the potential alteration of its plasticity in SCZ. We investigated the plasticity of PPS in SCZ patients after a motor training with a tool in the far space.** ***Study Design:*** **Twenty-seven SCZ patients and 32 healthy controls (HC) underwent an audio-tactile task to estimate PPS boundary before (Session 1) and after (Session 3) the tool-use. Parameters of PPS, including the size and the slope of the psychometric function describing audio-tactile RTs as a function of the audio-tactile distances, were estimated.** ***Study Results:*** **Results confirm a narrow PPS extent in SCZ. Surprisingly, we found PPS expansion in both groups, thus showing for the first time a preserved PPS plasticity in SCZ. Patients experienced a weaker differentiation from others, as indicated by a shallower PPS slope at Session 1 that correlated positively with negative symptoms. However, at Session 3, patients marked their bodily boundary in a steeper way, suggesting a sharper demarcation of PPS boundaries after the action with the tool.** ***Conclusions:*** **These findings highlight the importance of investigating the multisensory and motor roots of self-disorders, paving the way for future body-centred rehabilitation interventions that could improve patients' altered body boundary.**

Key words: bodily self/multisensory integration/plasticity/self-disorder/self-other boundaries

Introduction

A primary disruption of the so-called bodily self is considered a core feature of the psychopathology of schizophrenia.[1,2] Experiences of self-alienation, blurred self-other boundaries, disturbed corporeality, and altered stream of consciousness represent some of the critical features affecting the schizophrenic self. One possible and plausible process at the base of this disembodied self is an inefficient body-related multisensory integration process[3] which normally occurs also within the peripersonal space (PPS), the buffer zone immediately surrounding our body.[4] It has been suggested that PPS indexes the spatial self, ie, the experience of being a bodily self in space,[5–7] which contributes to the maintenance of a coherent representation of our basic sense of self in relation with the external world[8] and subtends our capacity of self-other distinction.[9–11] The individual extension of PPS is not fixed; it largely varies across people,[12] depending on several individual characteristics (eg, Refs. [13–15]). Besides the PPS extension, human and animal studies have revealed that this sector of space acts as an extremely adaptive and malleable border,[16] shaped by the different experiences (eg, Refs. [12,17–19]), including motor experiences such as the use of a tool in the far space that leads to the expansion of PPS boundaries.[20–24] From the electrophysiological studies on monkeys[23,25] to more recent evidence in humans,[24,26,27] it has emerged that the multisensory integration mechanisms underlie both the extension and plasticity of PPS phenomena. Evidence of significant abnormalities in PPS extension among schizophrenia patients is recently accumulating.[16,28,29] However, very little is known about its plasticity. Investigating not only the extent of PPS but also its malleability has both clinical and social relevance. Indeed, the boundaries of PPS are constantly changing due to the interactions we make with the stimuli surrounding our body, be they people, or

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objects. A suitably plastic space is functional for the organism to continuously integrate both exteroceptive and interoceptive signals in order to promptly react to them. Thus, better understanding of the functional property of PPS itself could elucidate not only the well-known social and motor impairments that characterize schizophrenia patients but it could give also insights on potential future rehabilitation protocols for such patients. To fill this relevant gap, we have investigated the plasticity of PPS in schizophrenia patients asking them to perform a motor training with a tool.[21] In order to assess the extension of PPS, both before and after the motor training phase, we used an audio–tactile interaction task[21,28] with approaching sounds. This approach, grounded in neurophysiology, offers a valid implicit method to quantify self–other boundary by estimating the parameters of PPS, such as the size and the slope of PPS, taking advantage from the sensorimotor nature of the PPS itself. Taking into account previous evidence of PPS impairments in schizophrenia[28] and the fact that differences in the sensory modality of the approaching stimuli (auditory vs visual) probably led to inconsistent findings in literature, we expected (1) to confirm the results obtained by Di Cosmo et al,[28] which showed narrower and steeper PPS boundary in schizophrenia patients than in controls, before the motor training; (2) based on existing evidence of multisensory integration deficits and motor abnormalities in schizophrenia (eg, Refs. [30–33]), a reduced or even absent PPS expansion, after the motor training.

Methods

Participants

Twenty-seven patients with schizophrenia (SCZ; 21 males, mean age 32.55 years, SE = 2.45) and 32 healthy control participants (HC; 14 males, mean age 28 years, SE = 2.73; age between groups difference: $t_{(57)} = -1.97$; $P = .08$) were included in the present study (table 1). Participants' handedness was assessed by the Edinburgh handedness inventory[34] (between groups difference: $t_{(57)} = 0.25$; $P = .80$). The total sample size exceeded the minimum amount required ($N = 54$) estimated by means of statistical a priori sample size calculation, obtained for repeated-measures ANOVA considering both within and between interactions ($1-ß = 0.95$, $\alpha = 0.05$, and effect size $f = 0.25$). Post hoc power estimation analysis conducted for repeated-measures ANOVA considering both within and between interactions including the actual effect size of our main effect ($f = 0.27$) and the final sample size ($N = 59$) confirmed the high achieved statistical power ($1-ß = 0.98$). SCZ participants were included in the study if they (1) received a diagnosis of Schizophrenia according to DSM-5 criteria; (2) reached the resolution of the acute phase of illness was reached, defined as the achievement of a clinical stabilization phase with initial symptom response and reduced psychotic symptoms severity.[35] The latter was described as a reduction in psychoticism dimension (ie, hallucinations and delusions) to a low to mild symptom intensity level[36]; (3) they provided a written informed consent to study participation. Diagnosis of schizophrenia was confirmed using the DSM-5 Axis I disorders (SCID-5-CV).[37] We assessed the severity of the main psychopathological dimensions in SCZ patients with the Positive and Negative Syndrome Scale (PANSS[38]), which measures symptoms severity in schizophrenia. All patients received medication based on a low–medium dose of a single atypical antipsychotic drug. To check for the potential effect of the pharmacological treatment on patients' performance, we converted patients' treatment in chlorpromazine equivalents.[39] No significant correlation was found (Supplementary Materials, section 1.1). Exclusion criteria for all participants were: (1) a current mental disorder related to a general medical condition or to drug or alcohol abuse or dependence; (2) a cognitive impairment which could affect the compliance with testing procedures; (3) touch or hearing anomalies. The study was approved by the Local Ethical Committee (AVEN) and was carried out in accordance with the Declaration of Helsinki (1964 and subsequent amendments).

Table 1. Demographic Information for SCZ and HC Groups and Clinical Scales of SCZ

		SCZ	HC
n		27	32
Male, *n*		21	14
Age, years		32.55; SE 2.45	28; SE 2.73
Edinburgh (Handedness)		0.67; SE 0.08	0.70; SE 0.04
Illness duration (mean; SE)		9.69 years; SE 2.23	n.a.
Age of onset (mean; SE)		23.22 years; SE 1.30	n.a.
Number of episodes (mean; SE)		2.33; SE 0.33	n.a.
Chlorpromazine equivalent dose (mean; SE)*		488.88 mg/die; SE 62.33	n.a.
Scales	**Subscales**		
PANSS (mean; SE)	Total	79.70; SE 3.63	n.a.
	Positive scale	14.33; SE 1.15	
	Negative scale	23.59; SE 1.22	
	General psychopathology scale	41.78; SE 2.21	

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Procedure

The experimental paradigm consisted of three sessions, following the procedure adopted in our previous study.[21] First, participants performed the peripersonal space task (ie, PPS task – Session 1) in order to measure the individual PPS boundary at baseline. After this session, they took part to Session 2 (ie, training phase, see below). Lastly, participants were submitted again to PPS task (Session 3) in order to measure PPS boundaries after actively using the tool. The entire procedure was carried out on the same day.

Sessions 1 and 3: PPS Task. The location of participants' PPS boundary was measured using an adapted version of the well-established PPS task procedure[40] used in our previous study.[21] The rationale behind this task refers to the PPS mapping itself, which is allowed through the integration of somatosensory information related to body parts and visual or auditory information related to objects presented in the sector of space surrounding the same body parts.[41] Thus, the task used here includes an audio-tactile stimulation as it has been shown that stimuli from different sensory modalities interact more effectively when presented within the same portion of space.[42] During the experiment the participants were blindfolded and comfortably seated at a table with the palm of their right hand resting on it (figure 1, Panel A). Participants were asked to respond as fast as possible to a tactile target, while an external auditory stimulus was presented either as static (flat sound) or as dynamic (looming sound). Although participants are instructed to focus on the tactile targets and to ignore the auditory stimulus, several studies showed that reaction times sped up as a function of the perceived distance of the external stimuli at the time of tactile stimulation.[11] The distance of the auditory stimulus from the participants' body at which this multisensory effect occurs—where reaction times to multimodal trials are significantly faster than those to unimodal tactile trials—is taken as a proxy of PPS representation. For a detailed description of the apparatus and procedure, please refer to the Supplementary Materials (Section 1.2).

Session 2: Active Tool-use. Session 2 was carried out following the procedure adopted in our previous study.[21] Specifically, participants were instructed to move 50 small coloured objects (green and red), placed on two marked areas of the table, in the far space (85 cm from participants' chest). Participants sat along the short side of the table and were requested to use a tool to grab and move one object at a time across the two areas. All objects were moved from one marked area to the other and then repositioned on the initial area for a total of 100 movements (figure 1, Panel B). Session 2 lasted around 10 min.

Data Analysis

We performed an analysis of variance (ANOVA) across sensory modalities in order to confirm that multisensory audio-tactile trials (regardless of distance) were faster than unisensory tactile trials, and thus as expected audio presentations facilitated tactile responses (eg, Ref. [43]; see

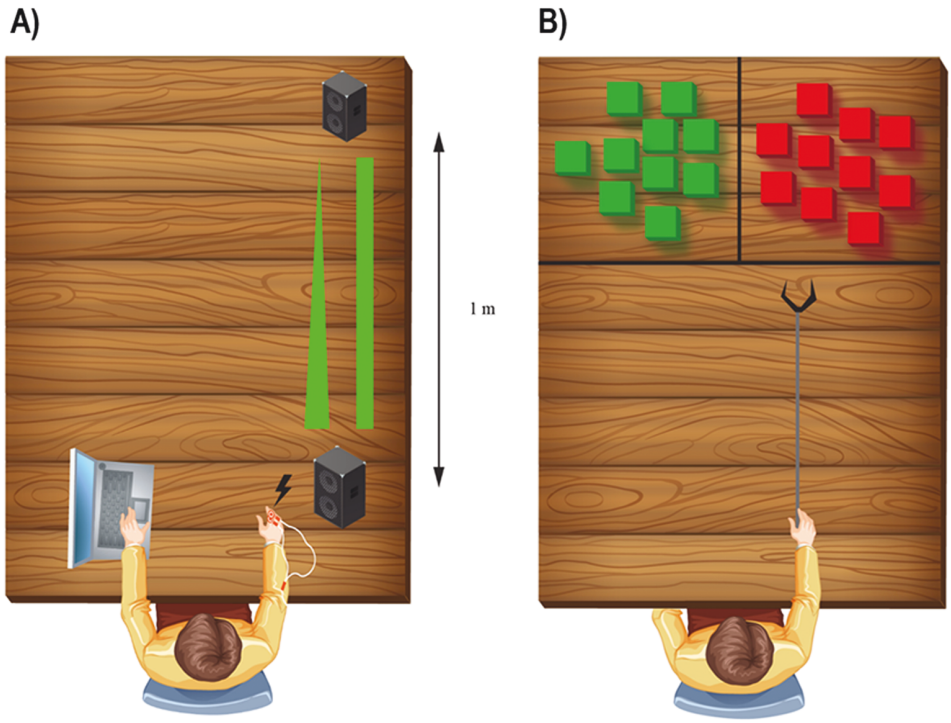

Fig. 1. Panel A) Experimental setting of PPS task. The shapes represent the two adopted sounds (rectangular shape = flat sound; triangular shape = looming sound). **Panel B)** Qualitative representation of the training phase.

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Supplementary Materials, Section 1.3). Next, to check the different modulation of looming compared to flat sounds on tactile reaction times (RTs) before performing the Sessions 2 (RTs measured at the baseline condition), an ANOVA was carried out. This was considered a preliminary step in order to proceed to consider only looming stimuli as experimental variables (Results Section 3.1). Lastly, to estimate the individual boundary of PPS, the central point (hereafter PSE, point of subjective equality) of the psychometric function describing audio-tactile RTs as a function of audio-tactile distance was measured via the Spearman–Karber (SK) method[44,45] in line with recent studies on PPS.[43,46] For more specific details about the implemented procedure, please refer to the Supplementary Materials (Section 1.4). Before proceeding to consider the whole sample, in order to verify the effectiveness of the procedure followed and check the expected PPS expansion among controls, we ran a series of analyses only on the control group (Supplementary Materials, section 1.5). Subsequently, an ANOVA was carried out both on PSE values and on the slope's values (hereafter DL, difference limen, estimated via the SK method) estimated in Session 1 and Session 3 respectively (Results section 3.2 and 3.3).

For all the analyses, whenever appropriate, significant differences were explored performing Newman–Keuls post hoc comparison. Partial eta-squared (η^2_p) was calculated as effect size measure. Moreover, the 95% nonparametric bootstrap confidence interval was estimated (1000 resamples).

Results

Multimodal Tactile RTs

We performed a repeated-measures ANOVA on mean RTs to tactile targets measured at baseline in order to verify the specificity of the effects of dynamic, compared to static stimuli on tactile RTs. Specifically, data were entered in a repeated-measures ANOVA with two within-subject factors, Sound (Looming, Flat) and Distance (D1, D2, D3, D4, D5) and Group (HC, SCZ) as between-subject factor. For RTs measurement, please consult the Supplementary Materials (Section 1.4). The ANOVA showed a significant main effect of Group ($F_{(1,57)} = 26.79$, $P < .001$, $\eta^2_p = 0.32$; HC: M = 307.94 ms, SE = 11.64; SCZ: M = 397.02 ms, SE = 12.67). Moreover, also the interaction Sound by Distance resulted significant ($F_{(4,228)} = 5.41$, $P < .001$, $\eta^2_p = 0.09$) showing that RTs were slower for looming compared to flat sounds at D1 (D1 looming: M = 346.97 ms, SE = 9.51; D1 flat: M = 332.05 ms, SE = 8.57; $P < .01$) whereas faster at D5 (D5 looming: M = 337.49, SE = 9.51; D5 flat: M = 346.65, 158 SE = 10; $P < .05$). This control analysis highlights the specificity of the effects of looming compared to flat stimuli on tactile RTs, in line with previous studies (eg, Refs. [20,21,28]).

Peripersonal Space Estimation

PSE values estimated in Session 1 (PSE-pre) and in Session 3 (PSE-post) were entered into ANOVA with Condition (PSE-pre, PSE-post) as within-subjects factor and Group (HC, SCZ) as between-subjects factor. Results showed a significant main effect of Group ($F_{(1,57)} = 8.91$, $P = .004$, $\eta^2_p = 0.135$) and of Condition ($F_{(1,57)} = 4.15$, $P = .043$, $\eta^2_p = 0.06$). Newman–Keuls post hoc carried out on the significant main effect of Group revealed that the PSE values of the HC group (HC: M = 1306.08 ms, SE = 33.76, 95% CI [4861, 10 093]), independently from the Condition, were significantly lower than the ones of the SCZ group (SCZ: M = 1455.03 ms, SE = 36.76, 95% CI [5777, 11 815]). Moreover, post hoc comparisons carried out on the significant main effect of Condition revealed that PSE-post values were significantly lower than the PSE-pre ones, thus showing a peripersonal space expansion after actively using the tool in the extra-personal space for both groups (PSE-pre: M = 1431.38 ms, SE = 34.74, 95% CI [5323, 11 052]; PSE-post: M = 1329.73 ms, SE = 35.81, 95% CI [5315, 10 856]) (figure 2). In other words, this analysis revealed that HC and SCZ differ both at Session 1 and Session 3 (main effect of Group) but both groups show a significant PPS expansion after the motor training. Indeed, in order to control for potential differences in terms of PPS expansion between the two groups, an independent sample t-test comparing the Delta PSE weighted values of both groups was performed. Delta PSE values were calculated first as the difference between PSE-post values relative to PSE-pre ones; then, we calculated the percentage of Delta PSE values relative to the PSE-pre values, in order to obtain Delta PSE weighted values, thus considering the different level of PSE-pre values that characterize both groups. Results revealed the

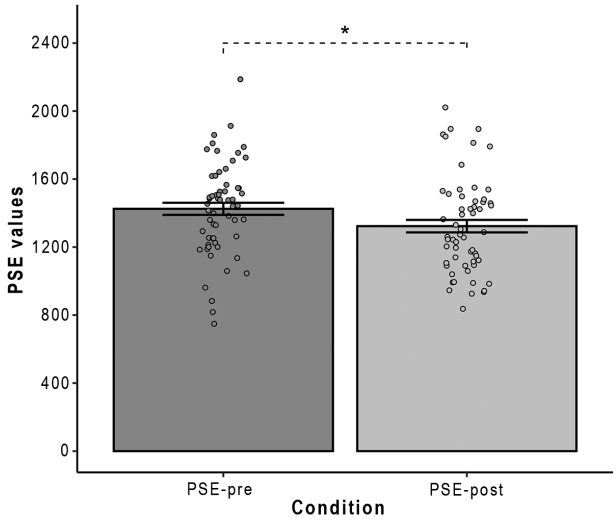

Fig. 2. Point of subjective equality (PSE) values measured in Session 1 and Session 3, for both Groups. Error bars depicted SE; * = $P < .05$.

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absence of significant difference between the two groups ($t_{(57)} = -1.08$; $P = .283$), thus confirming the equal PPS expansion in both groups. To ascertain whether the main results concerning the PPS expansion held on also with the traditional analyses, we ran a confirmatory analysis by measuring the central point following the sigmoidal function (Supplementary Materials, section 1.6).

For a representation of the psychometric curves via the SK method, for both groups, see Supplementary Fig.2.

Slopes Estimation

DL values measured in Session 1 (DL-pre) and in Session 3 (DL-post) were entered into ANOVA with Condition (DL-pre, DL-post) as within-subjects factor and Group (HC, SCZ) as between-subjects factor. Results showed a significant main effect of Group ($F_{(1,57)} = 16.65$, $P < .001$, $\eta^2_p = 0.23$; HC: M = 522.42 ms, SE = 21.95, 95% CI [2149, 5765]; SCZ: M = 654.86 ms, SE = 23.90, 95% CI [3011, 7049]) and of the significant interaction Condition by Group ($F_{(1,57)} = 6.03$, $P = .017$, $\eta^2_p = 0.09$). Interestingly, post hoc comparisons carried out on the significant interaction revealed that patients' DL-pre values were higher (SCZ DL-pre: M = 696.43 ms, SE = 30.88, 95% CI [3438, 7498]) than those of controls (HC DL-pre: M = 504.41 ms, SE = 28.37, 95% CI [1789, 5530]; $P < .001$; figure 3), highlighting that patients have a weaker bodily boundary (slower transition between one's own space and the external world) than controls, in line with previous studies (Ref. [29]). Moreover, patients' DL-post values were significantly lower (SCZ DL-post: M = 613.28 ms, SE = 28.76, 95% CI [2583, 6600]) than the DL-pre ones, suggesting that after the motor training with the tool, patients marked their bodily boundary in a steeper way. Lastly, no differences were found in DL-post values between the two groups ($P > .08$).

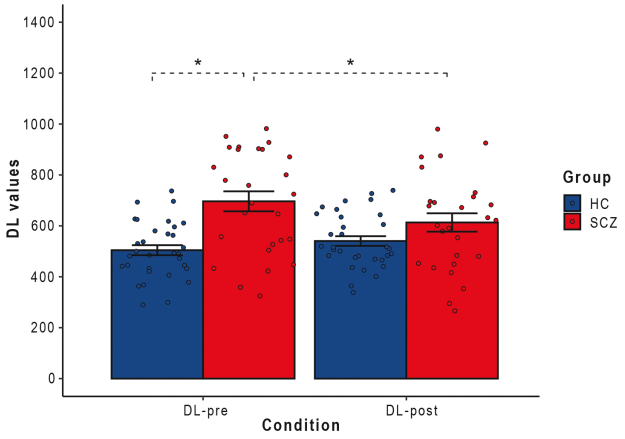

Fig. 3. Difference limen (DL) values measured in Session 1 and Session 3, for both Groups. Error bars depicted SE; * = $P < .05$. HC, Healthy controls; SCZ, Schizophrenia patients.

Correlations Analyses Between Clinical Data and Patients' PPS Measurements

Correlations between clinical data and PPS parameters (PSE-pre, PSE-post, DL-pre, DL-post values) were estimated by Pearson's correlation analyses. A significant positive correlation between PANSS negative subscale and DL-pre values was found ($r_{27} = 0.39$; $P = .043$, two-tailed) (figure 4). No other significant correlations were found (all $P_s > .09$).

Discussion

The present study investigated for the first time the plasticity of PPS in patients with schizophrenia. To accomplish this goal, participants underwent an audio–tactile interaction task[21,28] to measure individuals' PPS boundary both before and after a motor training session in which they used a tool to move small objects placed in the extrapersonal space.

Overall patients show higher PSE values at Session 1 and Session 3 with respect to controls (main effect of Group). This result confirms the narrower PPS extent (ie, higher PSE-pre values) in SCZ than in HC, in line with previous evidence,[28] and corroborates the same PPS under-sizing even following a motor training (see below). Moreover, patients showed a shallower PPS slope (ie, higher DL-pre values) at Session 1 with respect to controls, suggesting a weaker self-other differentiation. It is reasonable to hypothesize that the different methods (ie, sigmoidal fit vs SK method) used to estimate the PPS parameters may have differently biased the selection of patients leading to different results in terms of slope values. In fact, the new method applied here allows to include all participants in the analysis without excluding those not showing good sigmoidal fit, often due to flat distribution of the reaction times in our sample of patients. Interestingly, Paredes et al[47] recently proposed that the mechanism causing the sharper PPS boundaries observed in SCZ is a decrease of synaptic density. Based on

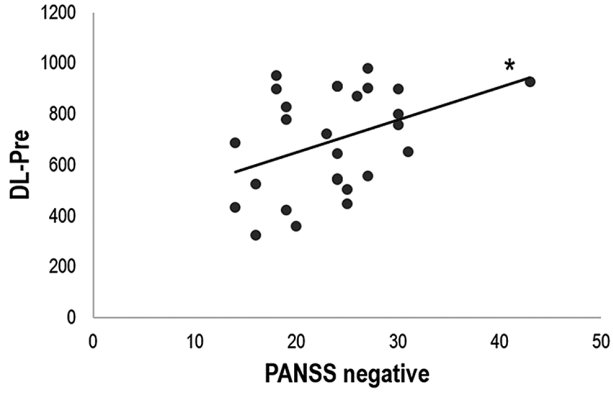

Fig. 4. Correlation plot of the relation between DL-pre values and PANSS Negative Symptoms Scale scores for SCZ patients. * = $P < .05$. DL, Difference limen.

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this model, shall we hypothesize a reduced alteration of this phenomenon in patients with shallower PPS boundaries? Future investigation is needed to answer this question. The paucity of the current data estimated with the SK method does not allow to give more robustness to our conclusions. Future studies could implement a new neural network model testing SCZ' data extracted with the SK method, which inevitably include patients with poor sigmoidal fitting, to unravel this skein. On the other hand, we should also take into consideration the results of the significant correlations between patients' PPS boundaries and negative symptoms. These results are coherent with those of Di Cosmo and colleagues[28] who found that the narrower the PPS, the greater the severity of negative symptoms. Taken together these results, suggesting a strict relation between bodily-self disturbances and the negative dimension, are particularly relevant as negative symptoms represent a core feature of schizophrenia psychopathology.[48] Accordingly, the recently developed Spatiotemporal Psychopathology theory,[49–52] by claiming that the brain provides the neuronal basis for our experience of time and space and the subsequent shaping of our sense of self, offers a promising interpretative framework that connects abnormal spatiotemporal integration with the discontinuous schizophrenic sense of self and the negative symptomatology.[53–55] However, given the limited available literature on the correlation between patients' symptomatology and PPS parameters,[16,28,29] future studies should address more thoroughly this issue.

A reduced PPS extension before and after a motor training does not necessarily also imply an altered PPS plasticity. Indeed, contrary to our initial assumptions, results showed a PPS expansion after the motor training with the tool in both groups, thus highlighting, for the first time, a preserved PPS plasticity in SCZ. Moreover, after the motor training, patients mark their bodily boundary in a steeper way similar to that of the controls (ie, we did not find any difference in the slopes values between Sessions 1 and 3 among controls) (see figure 5 for a schematic representation of the results).

Taken together, our findings show that the action itself plays a crucial role triggering not only the expansion but also the better demarcation of PPS boundaries after a motor training with a tool in the far space. On the one hand, this certainly emphasizes the already well-established role of the motor system in the mapping of PPS (eg, Refs. [4,12,56–60]), recently extended also by Ronga and colleagues[27] who have provided the first electrophysiological evidence of tool-use dependent plasticity in the human brain, showing the involvement of the premotor frontal and parietal areas in the expansion of PPS. Obviously, our data represent the first behavioral evidence of the preserved PPS plasticity in schizophrenia. Therefore, they should be taken with caution as well as the explanations behind this. Additionally, further studies are needed in order to answer to several outstanding

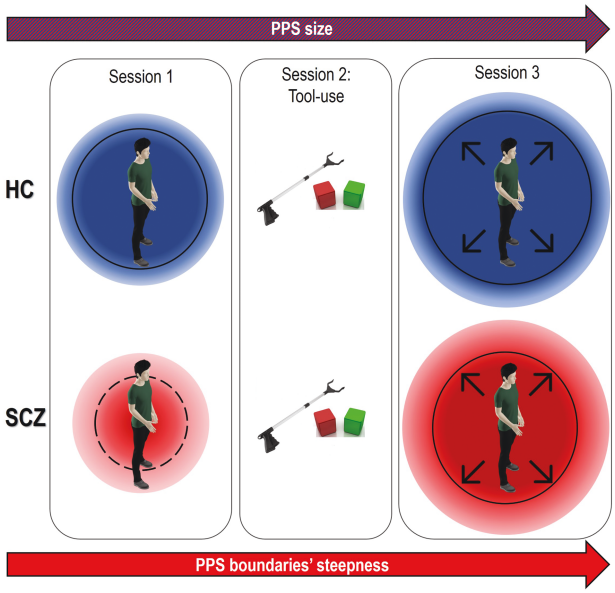

Fig. 5. Graphical representation of PPS size and boundaries' steepness in HC and SCZ. The PPS is larger and with sharper boundaries in HC than in SCZ at Session 1. After tool-use, at Session 3, the PPS is larger in HC than in SCZ but both groups show an equal PPS expansion (bold arrows). Only SCZ show steeper PPS boundaries at Session 3 compared with Session 1. The dashed and continuous circles indicate the shallowness and steepness of PPS boundaries, respectively. See the main text for the full explanation of the results.

issues, such as to clarify the mechanisms behind patients' PPS impairments; deeper understanding of the neural mechanism underlying PPS plasticity in the human brain can shed new light on the similarities and differences between the normal and psychopathological PPS mapping and plasticity.

Our new data certainly open up interesting scenarios also from a psychopathological point of view. Indeed, the present study provides further evidence of the anomalies of the spatial self in schizophrenia, helping to elucidate the roots of its phenomenal aspect and to grasp the basic anomalies from which more complex symptoms may arise. Furthermore, it fosters a deeper investigation of these anomalies that can in turn provide additional knowledge to the translational studies on the neural and biological bases of the schizophrenia phenotype. Motor disturbances are now considered a central feature in schizophrenia psychopathology and a putative endophenotype of the disorder.[61] In fact, they are detectable in the entire schizophrenia spectrum, including high-risk individuals and drug-naïve patients, long preceding the clinical onset.[62] On the other hand, our findings supporting a preserved motor plasticity in SCZ could suggest the persistence of deep biological motor patterns still responsive to motor stimulation, highlighting the key role of future targeted rehabilitation interventions.

This study has some limitations to consider. First of all, our data represent the first behavioral evidence of the

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preserved PPS plasticity in schizophrenia. Therefore, they should be taken with caution as well as the interpretations here offered. Moreover, even though the sample size is pretty high compared to the usual sample sizes found in several studies using this paradigm, is nonetheless modest and involving patients in stable phase of recovery, thus perhaps representative of only one phase of the disease process. Future studies might include first-episode patients and high-risk subjects to investigate more thoroughly space anomalies in these cohorts.

Finally, the slope data appear to be not entirely consistent with previous studies, thus highlighting the necessity of deeper investigations. Moreover, the data on the correlation between patients' weak boundaries and negative symptomatology spurs further elucidation in this regard. These data indeed could reveal a "subgroup" of patients characterized by a tighter but blurrier PPS potentially suggesting a reduced alteration of synaptic density decrease.[45]

In conclusion, the present study demonstrates, for the first time, the expansion and sharpness of the PPS boundaries after a sensory-motor training in schizophrenia, shedding new light on the understanding of the spatial self in psychopathology. Our findings demonstrate the relevance of the investigation of the multisensory and motor roots of self-disorders, paving the way for potential future body-centred rehabilitation interventions that could improve patients' weakened body boundary.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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