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Neural Correlates of Self-other Distinction in Patients with Schizophrenia Spectrum Disorders: The Roles of Agency and Hand Identity

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Schizophrenia spectrum disorders (SSD) are characterized by disturbed self-other distinction. While previous studies associate abnormalities in the sense of agency (ie, the feeling that an action and the resulting sensory consequences are produced by oneself) with disturbed processing in the angular gyrus, passive movement conditions to isolate contributions of motor predictions are lacking. Furthermore, the role of body identity (ie, visual features determining whether a seen body part belongs to oneself) in self-other distinction is unclear. In the current study, fMRI was used to assess the roles of agency and hand identity in self-other distinction. Patients with SSD and healthy controls (HC) performed active and passive hand movements (agency manipulation) while seeing their own or someone else's hand moving in accordance with their action (hand identity manipulation). Variable delays (0–417 ms) between movement and feedback had to be detected. Our results showed overall lower delay detection performances during active than passive conditions; however, these differences were reduced in patients when the own hand was displayed. On a neural level, we found that in HC, activation in the right angular gyrus was modulated by agency and hand identity. In contrast, agency and hand identity revealed no overlapping activation in patients, due to reduced effects of agency. Importantly, HC and SSD patients shared similar effects of hand identity in the angular gyrus. Our results suggest that disturbances of self-other distinction in SSD are particularly driven by agency, while self-other distinction based on hand identity might be spared.

Key words: action perception/angular gyrus/efference copy/fMRI/passive movement/prediction

Introduction

Schizophrenia spectrum disorders (SSD; ie, schizophrenia and schizoaffective disorder) manifest itself, among others, in an impaired distinction between self and other.[1] A central component of self-other distinction is the ability to experience oneself as the author of one's own actions and their resulting sensory consequences, also known as (sense of) agency.[2,3] It has been suggested that agency is governed by action-based predictive processing: Copies of the motor command (efference copies) are used to predict upcoming (re-afferent) sensory information.[4] Sensory events are perceived as externally produced if they deviate from the prediction.[5] Action-based predictive processing allows the brain to suppress the processing of sensory consequences arising from one's own actions, which is reflected by decreased perceived intensity[6] and reduced neural response in primary sensory areas[7–10] for actively vs passively generated sensory input. It has been shown that neural suppression effects are weaker in patients with SSD than healthy control subjects (HC),[11,12] indicating that impaired self-other distinction in SSD is linked to defective motor predictions.[13,14]

In addition to suppression effects in sensory areas, processing of agency and self-other distinction has been associated with activity in the posterior parietal cortex (PPC).[15–17] Specifically, the angular gyrus (AG) shows increased activation when a loss of agency is experienced.[3,18–23] Crucially, a lack of modulation of AG activity by agency has been demonstrated in schizophrenia.[24–26] However, previous studies mainly employed temporal or spatial deviations between movements and feedback to assess the role of motor predictions,[24,25,27] rendering it possible that the results reflect intersensory mismatch rather

than differences in motor predictions. Therefore, control conditions with passive movements are required to isolate the role of motor predictions in agency processing.

Body identity (ie, visual features indicating whether a body part belongs to oneself) represents a different way to distinguish self from other.[10] In a study with HC, we could show that processing of active vs passive hand movements in the AG is modulated by hand identity (handID).[10] While behavioral studies suggest that HC are adept at recognizing their own body parts,[28–30] findings are less consistent in patients with SSD. For instance, some studies reported worse performances in self-face recognition in patients with schizophrenia than HC,[31,32] while others found mixed[33] or no effects.[34,35] Overall, it is open whether patients with SSD show impairments in self-other distinction based on handID similar to those based on agency.

The current study investigated behavioral and neural correlates of self-other processing based on agency and handID in patients with SSD and HC. To assess the role of agency, participants performed active and passive hand movements. HandID was manipulated by presenting participants with a video showing their own or someone else's hand moving in accordance with their action. To measure perceptual suppression, participants had to detect delays between their movements and the feedback.[7,9,10,36,37] Based on the literature, we expected less modulation by agency for SSD patients than HC on the behavioral and neural level. Furthermore, we assumed that the AG is involved in self-other distinction and should thus be modulated by agency and handID; however, we predicted that modulation of AG activation by agency is reduced in SSD patients. For handID, both similar (if intact) and less (if impaired) modulation in SSD patients than HC in the AG was possible.

Materials and Methods

The methods of the current study are reported in detail elsewhere.[10]

Participants Forty-three patients with SSD and 23 HC were tested. Five patients and three HC were excluded from the sample (supplementary material S1). Thus, the final sample consisted of 38 patients (age: 22–56 years) with an attested ICD-10 diagnosis of schizophrenia ($n = 33$) or schizoaffective disorder (SAD; $n = 5$) and 20 HC (age: 20–55 years) without any psychiatric diagnosis. All HC and 20 patients participated in the fMRI experiment, while 18 patients participated in a behavioral session outside the scanner; see Experimental Design and Procedure for details. Patients with SAD were included, since symptoms of SAD resemble those of schizophrenia,[38–41] and previous research did not find significant differences in suppression effects between patients with schizophrenia and patients with SAD.[37,42] Groups were matched for age, sex, and educational degree (supplementary table S1). Only patients who were deemed stable for participation were invited. Therefore, patients were largely oligosymptomatic at the time of testing, as assessed by the scale for the assessment of positive symptoms[43] (*Mean*: 12.3, *SD*: 10.9; see also supplementary material S3, for limitations). All participants gave informed consent and were compensated for participation. The experiment was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

Stimuli and Equipment Participants performed right hand movements while holding the handle of a movement device (supplementary figure S1). The handle could be moved from the left to the right and back again along a circular arc (trajectory: 5 cm). Either participants actively moved the device with their hand, or their hand was passively moved by the device using air pressure. On 50% of the trials ("self" trials), the participant's own hand was recorded with a high-speed camera (MRC High Speed, MRC Systems GmbH, Heidelberg, Germany; refresh rate: 4 ms) and played back onto a computer screen (refresh rate: 60 Hz). In the other 50% of the trials ("other" trials), male participants were presented with the hand image of a female person (and vice versa) holding the device. The image of the "other" hand directly followed the participant's actual movement. Between the onset of the actual and displayed movement, delays (0, 83, 167, 250, 334, or 417 ms + internal setup delay of 43 ms) were randomly inserted.

Experimental Design A mixed design with the between-subjects factor group (HC vs SSD) and the within-subjects factors agency (active vs passive) and handID ("self" vs "other") was used, resulting in four conditions for each group: active self, passive self, active other, passive other (figure 1). The study encompassed a preparatory session in which participants were familiarized with the setup. In a separate fMRI session, two runs were carried out, each consisting of 48 trials (two trials per delay for each condition). If patients were unable to go into the MRI scanner, they completed a behavioral session outside the scanner instead ($n = 18$). Each run was divided into an active and a passive block starting with a cue ("Active" or "Passive"). The start of individual trials was indicated by a cue ("Ready."), after which a hand ("self" or "other") was displayed. "Self" and "other" feedback was randomized. In active trials, participants could execute the movement at any point during the time a hand was visible. In passive blocks, the movement device was programmed to initiate the movement 500 ms after the onset of the hand display. Thereafter, a cue ("Delay?") signaled participants to respond via button press (left index or middle finger) whether the feedback was perceived as delayed or not. Trials ended with the screen turning black.

Procedure Participants were instructed to hold the movement device with their right hand such that the upper part of the handle was held by the index finger and the thumb, with the remaining fingers touching the lower part of the grip (supplementary figure S1). Movements

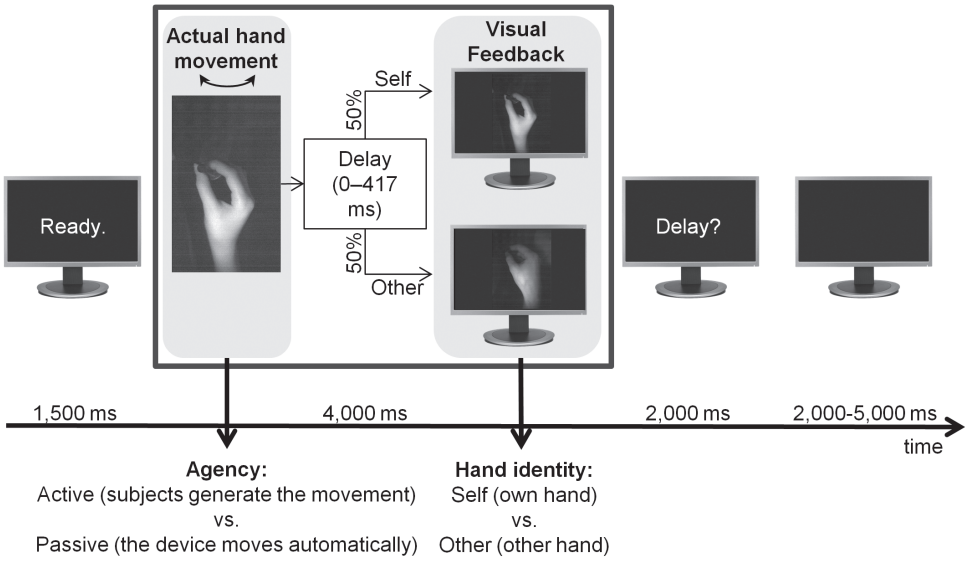

Fig. 1. Experimental paradigm (adapted from Ref.[10] [https://creativecommons.org/licenses/by/4.0/]). Participants performed active or passive hand movements while seeing their own or someone else's hand moving in accordance with their action. Delays inserted between movements and feedback had to be detected by the participants.

were performed by extending and subsequently returning the wrist to a neutral position while holding the handle. Movements had to be completed in about 1.5 s. In passive blocks, participants were asked to let their hand be moved by the device. All procedures were practiced in the preparatory session. During the preparatory (all participants) and the behavioral session (n_{SSD} = 18), participants sat in front of a computer screen. The movement device was placed on a table, such that it could be reached with the right hand while resting the arm on the table. Right hands were obstructed from view by a curtain. In the fMRI session (n_{HC} = 20; n_{SSD} = 20), participants lay supine in the MRI scanner, with the movement device placed next to the right thigh. The visual feedback was displayed on a screen which participants saw via a tilted mirror. After the scanning or behavioral session, respectively, participants were handed out a handID questionnaire (supplementary material S5).

Functional Data Acquisition A 3 T Magnetom Trio Tim scanner (Siemens, Erlangen, Germany) and a 12-channel head-coil were used for MRI data acquisition. To acquire functional data, a T2*-weighted gradient-echo echoplanar imaging sequence was applied (repetition time [TR]: 1,650 ms, echo time [TE]: 25 ms, flip angle: 70°). Three hundred and thirty volumes, each covering the brain in 34 axial slices (matrix: 64 × 64, field of view [FoV]: 192 mm × 192 mm, slice thickness: 4 mm, voxel size: 3 mm × 3 mm × 4.6 mm [including a gap of 0.6 mm]), were acquired during each run in descending order. A T1-weighted MPRAGE sequence (TR: 1,900 ms, TE: 2.26 ms, flip angle: 9°) was used for anatomical image acquisition (matrix: 256 × 256, FoV: 256 mm × 256 mm, slice thickness: 1 mm, voxel size: 1 mm × 1 mm × 1.5 mm [including a gap of 0.5 mm]).

Behavioral Data Analysis Trials were excluded from the behavioral analysis if no movement was executed (0.3% of all trials) or no response was registered (0.7% of all trials). To check whether participants used the correct key for delay responses, mean delays for "yes" and "no" responses were calculated (supplementary material S6).[8] Since it is more likely to respond "yes" for longer than for shorter delays, lower mean delays for "yes" than "no" responses in all conditions indicated that the participant used the wrong button assignment. In this case, all delay responses were swapped prior to analysis (n = 4; see also supplementary material S7, for robustness analyses omitting participants whose button assignment were flipped, yielding highly similar behavioral and fMRI results). Percentage of "yes" responses for each condition and participant were entered into a mixed ANOVA run in R (version 3.6.3).[44]

Imaging Data Preprocessing and Analysis For data preprocessing, standard routines of Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, University College London, UK) implemented in MATLAB 8.3 (The Mathworks Inc., 2014) were used. Data preprocessing encompassed realignment, coregistration between anatomical and functional images, segmentation, normalization to the Montreal Neurological Institute (MNI) standard space (resampled to a voxel size of 2 mm × 2 mm × 2 mm), and smoothing (8 mm × 8 mm × 8 mm full width at half-maximum Gaussian kernel). Framewise displacement between consecutive volumes was calculated.[45] In none of the runs, more than 10% of framewise displacement values exceeded 1 mm. For each participant, the general linear model was applied to define regressors of interest modeling the blood oxygenation level-dependent

(BOLD) response during the time a hand was displayed on the screen for each experimental condition. Regressors of interest were only constructed for trials in which a movement was registered. Six motion parameters as well as regressors modeling the BOLD signal during the presentation of cues and delay questions were included as nuisance regressors. All regressors were convolved with the canonical hemodynamic response function (HRF). The first derivative of the canonical HRF was also included in the model. A 128 s high-pass filter was applied to remove low-frequency noise from the time series. Regressors of interest were contrasted against the implicit baseline for each participant. The resulting contrast estimates were entered into a full factorial model on group level.

We first analyzed commonalities between agency (passive > active) and handID (other > self) within each group, then we investigated commonalities and differences regarding these factors across groups. We assumed that in HC, the AG is involved in distinguishing other from self and should therefore be modulated by agency and handID, resulting in overlapping activation for both factors: [(HC passive > HC active) ∩ (HC other > HC self)]. In patients, we expected impaired self-other distinction in the AG, leading to absent overlap: [(SSD passive > SSD active) ∩ (SSD other > SSD self)]. The absent overlap was expected to be caused by reduced effects of agency in patients, as assessed by a directed interaction contrast [(HC passive > HC active) > (SSD passive > SSD active)]. In contrast, modulation of AG activation by handID might be preserved in patients: [(HC other > HC self) ∩ (SSD other > SSD self)]. To test for differences between groups with regard to handID, we additionally constructed a directed handID × group interaction contrast [(HC other > HC self) > (SSD other > SSD self)]. For completeness, we also explored the overlap of agency effects across groups: [(HC passive > HC active) ∩ (SSD passive > SSD active)]. Finally, we exploratively investigated hand agency × handID × group interaction effects {[(HC active other vs HC active self) vs (HC passive other vs HC passive self)] vs [(SSD active other vs SSD active self) vs (SSD passive other vs SSD passive self)]} using *F*-contrasts, followed by directional *t*-contrasts if revealing significant clusters.

To calculate the minimum cluster size that ensures correction for multiple comparisons at $P < .05$, assuming an individual voxel type I error of $P = .005$, a Monte-Carlo simulation with 10,000 iterations was run (cluster_threshold_beta.m: https://osf.io/3wf7b/, downloaded on June 8, 2020).[46,47] A cluster extent threshold of 104 resampled voxels was obtained (estimated smoothness of the functional data: 9 mm; img_xcorr.m: https://osf.io/3wf7b/). To analyze common activations, the overlap from independently significant and Monte-Carlo corrected activation maps was investigated (minimum cluster size for overlap: 10 voxels).[48] Peaks and locations within overlapping clusters were identified using minimal *t*-statistics of the respective contrasts. Locations of peak voxels were labeled using the automated anatomical labeling atlas 3.[49] All coordinates are listed in MNI space.

Results

Behavioral Results

Behavioral analyses were based on the fMRI and the behavioral sample ($n_{HC} = 20$; $n_{SSD} = 38$). Behavioral results are displayed in figure 2. Significant effects were observed for the main effect of agency, $F(1, 56) = 17.4$, $P < .001$, $\eta_p^2 = 0.24$, the agency × group interaction effect, $F(1, 56) = 5.6$, $P = .021$, $\eta_p^2 = 0.09$, as well as the agency × handID × group interaction effect, $F(1, 56) = 5.5$, $P = .022$, $\eta_p^2 = 0.09$. Bonferroni corrected paired *t*-tests showed that HC gave significantly fewer "yes" responses during active than passive trials when seeing "self", $t(19) = -4.0$, $P = .005$, $d = 0.83$, and "other" hand feedback, $t(19) = -3.0$, $P = .010$, $d = 0.78$. In patients, the active–passive difference was significant during "other", $t(37) = -4.0$, $P = .005$, $d = 0.57$, but not during "self" trials, $t(37) = 0.06$, $P > .999$, $d < 0.01$. The ANOVA yielded no further significant effects, all $F(1, 56) \leq 3.0$, $P \geq .086$, $\eta_p^2 \leq 0.05$. No significant effects of session (ie, fMRI vs behavioral) were observed (supplementary material S8). For exploratory correlation analyses, see supplementary material S9.

fMRI Results

Overlap between Agency and handID Main effects of agency and handID for each group are listed in supplementary material S10. In HC, there were overlapping effects of agency and in the right MTG (*x*: 46, *y*: −52, *z*: 14, $k_E = 287$) and left supramarginal gyrus (SMG; *x*: −52, *y*: −50, *z*: 24, $k_E = 231$), including the right (*x*: 56, *y*: −58, *z*: 36) and left AG (*x*: −40, *y*: −52, *z*: 28), respectively (figure 3). Further overlap was found in temporal (right MTG: *x*: 62, *y*: −28, *z*: −2, $k_E = 284$; right inferior temporal gyrus: *x*: 44, *y*: −50, *z*: −12, $k_E = 95$), frontal (left inferior frontal gyrus: *x*: −50, *y*: 28, *z*: 18, $k_E = 215$), and occipital (left superior occipital gyrus [SOG]: *x*: −12, *y*: −86, *z*: 24, $k_E = 259$; left lingual gyrus: *x*: −14, *y*: −74, *z*: −6, $k_E = 115$; left inferior occipital gyrus [IOG]: *x*: −42, *y*: −72, *z*: −10, $k_E = 112$). There was no overlap between effects of agency and handID in patients at the original or a more liberal ($P < .005$, uncorrected, minimum cluster size: 10 voxels) threshold.

Group Effects of Agency Overlapping effects of agency across groups were observed in the bilateral cerebellum (*x*: −14, *y*: −70, *z*: −26, $k_E = 528$), the left STG (*x*: −52, *y*: −36, *z*: 20, $k_E = 133$), the right middle cingulate cortex (*x*: 8, *y*: 2, *z*: 36, $k_E = 215$), the right middle occipital gyrus (MOG; *x*: 40, *y*: −70, *z*: 4, $k_E = 154$), the left cuneus (*x*: −16, *y*: −62, *z*: 22, $k_E = 107$), the left anterior cingulate cortex (*x*: −6, *y*: 4, *z*: 30, $k_E = 13$), the left precuneus (*x*:

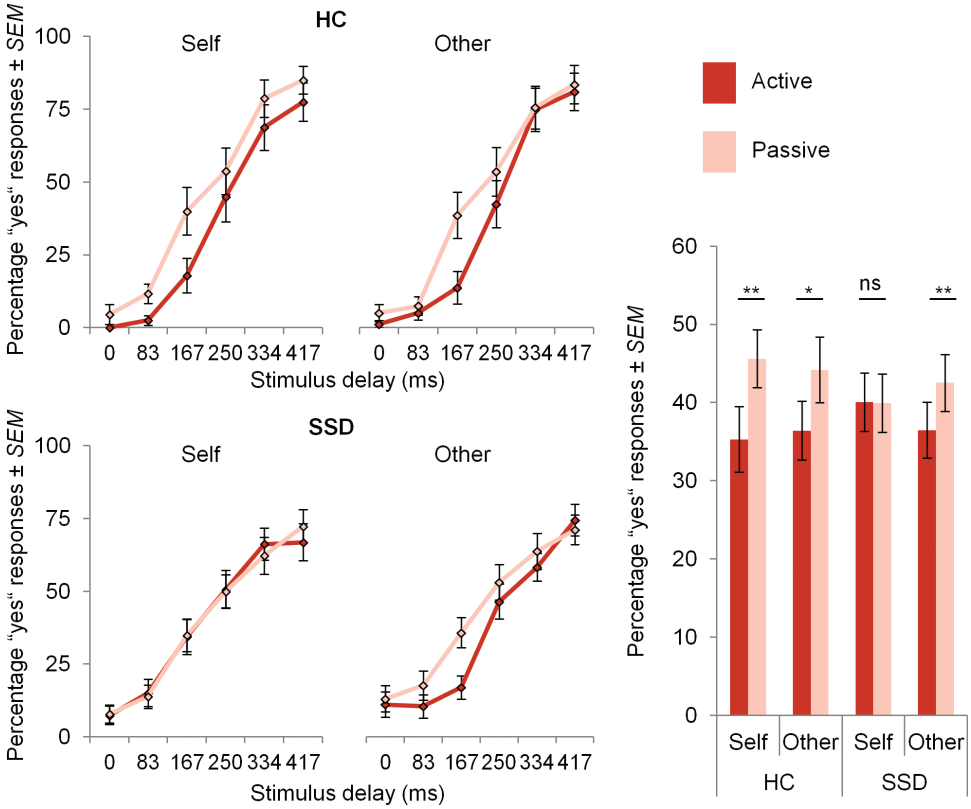

Fig. 2. Behavioral results. *$P < .05$; **$P < .01$; ns: not significant. $n_{HC} = 20$; $n_{SSD} = 38$.

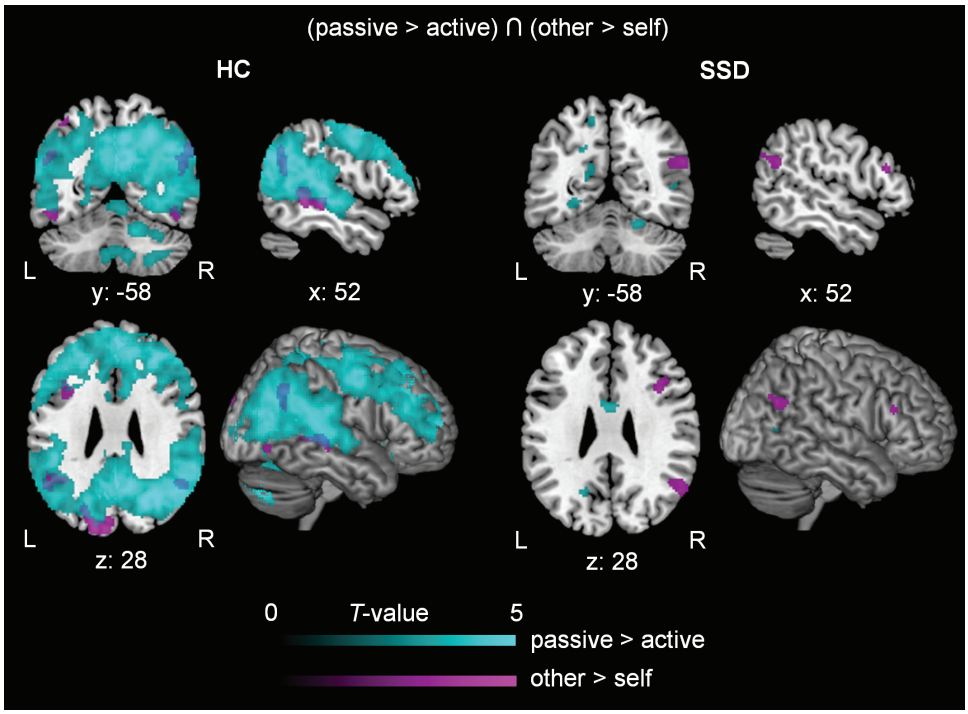

Fig. 3. Overlap between effects of agency and handID. There was no overlap in SSD patients. $n_{HC} = 20$; $n_{SSD} = 20$.

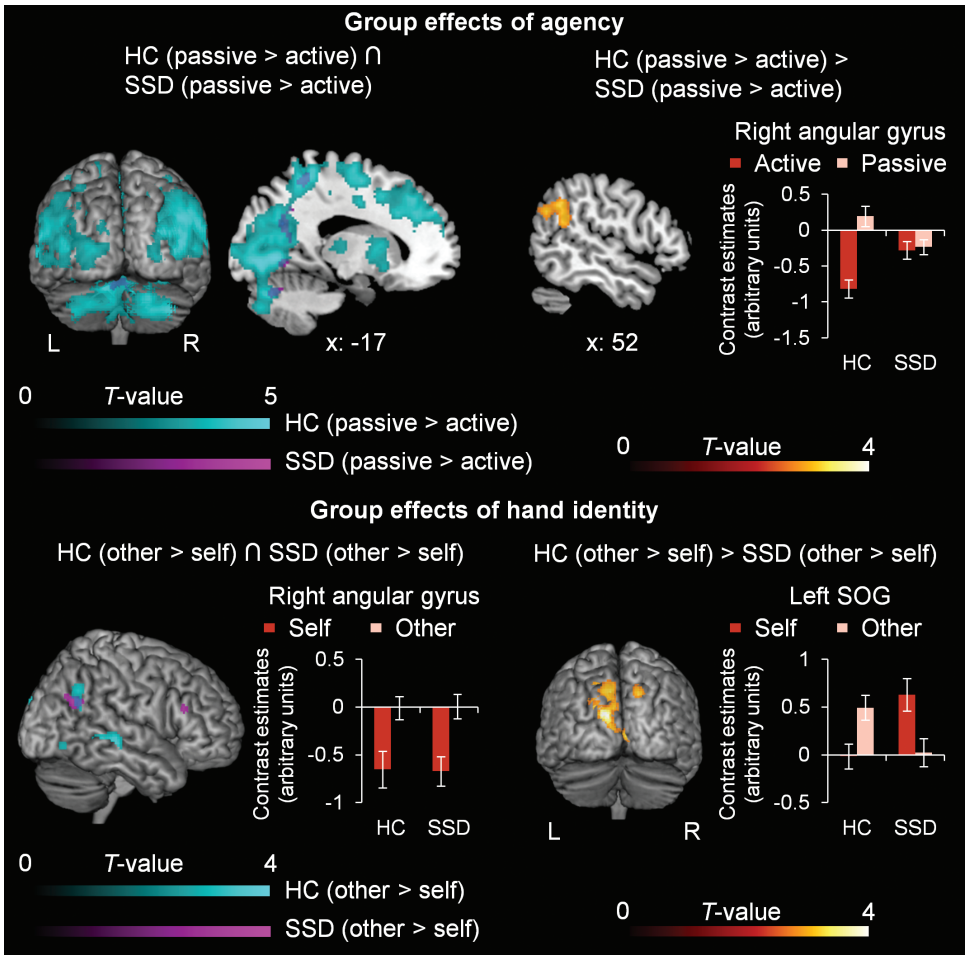

Fig. 4. Group level fMRI results. n_{HC} = 20; n_{SSD} = 20. For exploratory correlation analyses, see supplementary material S11.

Table 1. Anatomical Locations of Agency × Group and handID × Group Interaction Effects

Anatomical Locations (Local Maxima)	Hemisphere	*x*	*y*	*z*	*T*	No. Voxels
Agency × group						
Putamen	Left	−26	4	4	4.03	211
Cuneus (fusiform gyrus, lingual gyrus)	Right	22	−72	26	3.84	751
Putamen	Right	24	12	6	3.79	434
Supramarginal gyrus (angular gyrus)	Right	58	−48	24	3.75	616
Insula (superior temporal gyrus)	Right	28	−28	14	3.67	172
Middle occipital gyrus (calcarine sulcus)	Left	−26	−76	0	3.43	262
Supplementary motor area	Right	6	−2	50	3.21	205
Precuneus (posterior cingulate cortex, cuneus)	Left	−4	−66	28	2.99	141
handID × group						
Superior occipital gyrus (calcarine sulcus)	Left	−12	−92	20	4.40	1053
Cuneus (superior occipital gyrus)	Right	16	−82	38	3.22	142

Note: Labels in brackets denote local maxima of the cluster extent. n_{HC} = 20; n_{SSD} = 20.

−16, *y*: −48, *z*: 62, k_E = 75), and the left lingual gyrus (*x*: −20, *y*: −62, *z*: −4, k_E = 58; figure 4). Importantly, the agency × group interaction contrast revealed that in the right SMG, extending to the right AG, the passive > active difference was stronger in HC than in patients (table 1 and figure 4).

Group Effects of handID Overlapping effects of handID across groups were observed in the right AG (*x*: 52, *y*: −58, *z*: 28, k_E = 83). Furthermore, the handID × group interaction contrast revealed that in the bilateral SOG and the right cuneus, the other > self difference was stronger in HC than in patients (table 1 and figure 4).

Interaction between Agency, handID, and Group A directional interaction contrast revealed that in the left caudate nucleus, the right MOG, and the bilateral precuneus, the other > self difference was stronger during passive than active movements in HC. This pattern seemed to be reversed in patients (supplementary material S12).

Discussion

In the current study, we investigated commonalities and differences between HC and SSD patients in the processing of self-other distinction based on agency and handID. Our results suggest that self-other distinction in the right AG based on agency is impaired in SSD, while self-other distinction based on handID might be preserved.

The behavioral and neural data indicate that sensory suppression of actively generated visual movement feedback is reduced in patients with SSD, replicating studies using somatosensory[11,12,50] and auditory stimuli.[51] This supports the idea that compromised self-other distinction in SSD is associated with imprecise predictive processing due to dysfunctional efference copies, which may impair cancellation of sensory information arising from one's own actions.[27,52] Importantly, we contrasted active and passive movements, thereby isolating the role of the efference copy.[53] Interestingly, behavioral data revealed specifically reduced active–passive differences in patients with SSD for "self" feedback. This pattern indicates that predictive processing in SSD patients might be less affected for feedback displaying external, "non-self" objects, which would corroborate the assertion that SSD are disorders of "the self."[54–56]

Furthermore, our results indicate that in HC, the AG is involved in self-other distinction based on both agency and handID. In patients with SSD, however, modulation of activation in the AG by agency was decreased, whereas modulation by handID was similar to HC. This corroborates previous studies demonstrating impaired modulations of AG activity by agency in schizophrenia.[24–26] Crucially, impaired agency has been directly associated with self-disturbances in SSD.[2,4,57–62] Moreover, while behavioral studies on visual self-recognition have not revealed clear evidence for differences between HC and patients with schizophrenia,[32,34] strong group differences have been reported in action recognition studies.[24,63,64] In this sense, our results correspond to findings that patients with schizophrenia rely more on external (eg, handID) than internal signals (eg, motor predictions) when discriminating other from self.[65] This has been explained by multifactorial weighting models, where agency attribution emerges from the weighting of lower-level (sensorimotor) and higher-level (contextual/environmental) cues.[66–69] In SSD patients, imprecise efference copies render sensorimotor cues unreliable, thereby shifting more weight to contextual cues. In line with this, abnormal resting state activity and spatiotemporal integration in the default mode network (DMN), which has been associated with self-referential processing,[70–72] has been shown in subjects with psychosis-like symptoms.[73,74] It has been suggested that decreased anticorrelations between DMN activity and activity in the central-executive network, which is associated with the processing of exogenous stimuli,[75] may serve as a basis for the development of agency dysfunctions and self-disturbances in schizophrenia by blurring the border between self and other.[76,77] Similarly, it has been proposed that altered spontaneous neural activity in schizophrenia may alter the experience of one's self by changing the perception of the world, which may be linked to core symptoms of schizophrenia.[56,78]

Moreover, studies showed that the AG and the SMG are involved in the computation of movement plans.[79,80] Interestingly, it has been reported that patients with SSD perform poorer in gesture production tasks than HC, which may be linked to aberrant motor planning and monitoring.[81] These dysfunctions during gesturing can be improved by transcranial magnetic stimulation of the right inferior parietal lobule[82] and correlate with regions including the right AG/SMG.[83–85] Thus, we speculate that abnormal modulation of AG/SMG activity by agency may affect motor control in patients with SSD.

In the bilateral SOG and the right cuneus, HC showed lower activation for "self" than "other" feedback, whereas SSD patients showed an opposite pattern. Both regions have been reported to be involved in the dorsal visual stream, which is associated with visuomotor control.[86,87] Therefore, we speculate that HC seem to need less effort than SSD patients to monitor movements that involve their own hands, presumably due to effective predictive processing involving self-body parts.[10]

In conclusion, our results suggest that disturbances of self-other distinction in SSD may be particularly driven by agency disturbances, while self-other distinction based on handID might be spared.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Data availability

Data supporting the findings of the publication are available at Uhlmann et al.[88]

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