Agency Deficits in a Human Genetic Model of Schizophrenia: Insights From 22q11DS Patients

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Schizophrenia is a chronic and disabling mental illness characterized by a disordered sense of self. Current theories suggest that deficiencies in the sense of control over one’s actions (Sense of Agency, SoA) may underlie some of the symptoms of schizophrenia. However, it is not clear if agency deficits are a precursor or a result of psychosis. Here, we investigated full body agency using virtual reality in a cohort of 22q11 deletion syndrome participants to address this deficit with a genetic predisposition for schizophrenia. In two experiments employing virtual reality, full body motion tracking, and online feedback, we investigated SoA in two separate domains. Our results show that participants with 22q11DS had a considerable deficit in monitoring their actions, compared to age-matched controls in both the temporal and spatial domain. This was coupled with a bias toward erroneous attribution of actions to the self. These results indicate that nonpsychotic 22q11DS participants have a domain general deficit in the conscious sensorimotor mechanisms underlying the bodily self. Our data reveal an abnormality in the SoA in a cohort with a genetic predisposition for schizophrenia, but without psychosis, providing evidence that deficits in delineation of the self may be a precursor rather than a result of the psychotic state.

Key words: sense of agency/velocardiofacial syndrome/sensorimotor prediction/virtual reality/psychosis/locomotion

Introduction

Schizophrenia is a widespread and devastating psychiatric condition with a prevalence of over 1% of the population worldwide.1 Schizophrenia has been linked to abnormal mental states including a deterioration of cognitive and emotional processing and the manifestation of hallucinations and delusions. These symptoms are characterized by a diminished demarcation of self-other boundaries causing misattributions of self-generated perception, thoughts, and actions to external sources and vice versa.2,3 It has been suggested that this deficiency in the delineation of the boundaries of the self in schizophrenia is due to abnormal sensorimotor prediction mechanisms, causing a loss of agency for actions and thoughts.4–9 The putative mechanism for the Sense of Agency (SoA) is based upon the comparison of predictions regarding the sensory outcomes of self-generated actions (ie, efference copy) with afferent sensory signals.10–12 When the predictions and actual sensory signals match, a SoA over the action arises and the sensory signal is attenuated13–15 yet if a discrepancy is found it indicates that the sensory signals may be of external origin.16 Several studies have demonstrated aberrant sensorimotor prediction in schizophrenia patients, leading to erroneous agency,6,17–19 as well as a reduction of typical sensory and neural attenuation for self-generated actions,20–23 thereby linking altered sensorimotor prediction with positive, first rank symptoms of schizophrenia.2,24–26
Abnormal sensorimotor predictions underlying the SoA have been reported for schizotypal participants but with mixed results.\textsuperscript{37-39} Thus, while sensorimotor prediction deficits have been found across the schizophrenia spectrum, it is still unclear if they are a precursor to or a consequence of the psychotic state.

In the present article, we compared sensorimotor prediction abilities underlying the SoA in young individuals with 22q11.2 deletion syndrome (22q11DS) and typically developing adolescents. 22q11DS is the most common interstitial deletion in humans\textsuperscript{40} and is associated with increased (~30\%) risk for psychosis and schizophrenia.\textsuperscript{31,32} It is typically characterized by a 3Mb microdeletion\textsuperscript{33} containing about 60 genes. Several of these genes have been associated with phenotypical characteristics of 22q11DS, such as palate and cardiac malformations.\textsuperscript{34} Other genes have also been suggested as candidates for brain dysfunctions and psychiatric abnormalities such as psychosis.\textsuperscript{35} Indeed, 22q11DS has been suggested to be among the highest risk factors for schizophrenia spectrum disorders.\textsuperscript{36} Most clinical features of schizophrenia in individuals with 22q11DS are similar to idiopathic forms\textsuperscript{37,38,39}, but there is some evidence for earlier onset in 22q11DS individuals.\textsuperscript{32} 22q11DS is further characterized by atypical brain development possibly contributing to the presence of atypical self-related processes.\textsuperscript{38,39} For example, hypoactivation of cortical midline structures and striatum was found in 22q11DS during self-related processing compared to healthy controls.\textsuperscript{39}

To test if abnormalities in the SoA are already present in 22q11DS individuals who do not meet the criteria for a psychotic disorder, we employed two paradigms utilizing full body motion capture and online visual feedback with virtual reality. Previous studies have suggested that SoA deficits in schizophrenia may relate to deficits in temporal perception\textsuperscript{40-42}, differences in SoA under spatially conflicting conditions have been linked to imprecise sensorimotor predictions and an increased reliance on visual feedback.\textsuperscript{24,43,44} Consequently, we tested SoA in both temporal and spatial domains.

The first experiment tested sensorimotor predictions in the spatial domain using an established paradigm\textsuperscript{45-47} in which angular deviations between the participants’ movements and those of the virtual avatar are introduced. SoA was assessed by measuring participants’ judgments of control over the avatar’s actions for different levels of deviations.\textsuperscript{45,48,49} Based on these prior studies, we hypothesized that (i) all participants would correct their on-going movements to reach the target, (ii) detect large, introduced deviations but that (iii) group differences may arise for intermediate deviations of 7.5–15°. Explicit SoA judgments may be considered metacognitive decisions based on sensorimotor signals\textsuperscript{50,51} and metacognitive abilities have been suggested to be impaired in psychosis.\textsuperscript{52,53} To investigate both aspects, we additionally recorded confidence ratings of SoA judgments. As before, trials with intermediate deviations are of strongest interest as they have been linked to over- attribution of deviated feedback.

In the second experiment, we tested temporal sensorimotor predictions. Participants walking on a treadmill viewed an avatar walking on a similar treadmill, whereas temporal delays between their walking movements and those of the avatar were introduced and their SoA over the avatar’s movements was tested. In this paradigm, based on prior studies on temporal gait feedback,\textsuperscript{54,55} we expected to observe a U-shaped response pattern for the SoA, as both real-time trials and trials with delays close to the stride-time of the participant, would appear to be in-synch with the participants on-going movements. In both paradigms, motor performance (corrective movements and spatiotemporal gait characteristics) was quantified to ensure that differences observed in SoA are not due to differences in the performance of the motor task.

\section*{Materials and Methods}

\subsection*{Participants}

Forty-two participants (25 female) with a mean age of 18 ± 6 years were recruited for the study. Twenty-one participants had a genetically confirmed diagnosis of 22q11DS (13 female, 19 ± 7 years) whereas the other 21 were typically developing adolescents (12 female, 16 ± 4 years). Twenty control and \( N = 16 \) participants with 22q11DS completed study 1; \( N = 21 \) control and \( N = 17 \) participants with 22q11DS completed study 2 (see table 1 and supplementary material for details). Sex was closely matched across the two studies (both \( \chi^2 < 0.001, \text{df} = 1, P = 1 \), and no significant age difference was observed (both \( P > 0.05 \)). 22q11DS participants were relatively high functioning. The study was conducted according to the principles expressed in the Declaration of Helsinki and was reviewed and approved by the local ethics committee (University Hospital Lausanne, Switzerland). All participants or their legal guardians provided written informed consent for the collection of data and subsequent analysis.

\subsection*{Experimental Setup}

The two experiments are based on our previously published paradigms investigating SoA and sensorimotor control of walking during spatial\textsuperscript{55,47} or temporal conflicts\textsuperscript{54,55} in a virtual reality paradigm. In the first case, this involved introducing a randomized spatial deviation during a goal-directed walking task (over-ground); in the second case, it involved participants walking on a treadmill while the feedback of their own movement was played back with a randomized temporal delay. Technical details are described in the supplementary material.

\subsection*{Study 1}

\textbf{Procedure.} Study 1 followed the procedure described in\textsuperscript{46,47} but adapted to the capacities of adolescents.
Table 1. Baseline Characteristics of the Participants

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Note: Edu, (years of) education; SIPS, Structured Interview for Psychosis-Risk Syndrome; ADHD, Attention Deficit Hyperactivity Disorder; APS, Attenuated Psychosis Syndrome; GAD, General Anxiety Disorder; GRFD, Genetic Risk and Functioning Deterioration Syndrome; MDD, Major Depressive Disorder.

1Did not complete behavioral studies.
2Only completed the study with angular deviations.
3Only completed the study with temporal delays.

(reduced number of targets and deviations). Participants were given time to move freely in the VR environment, familiarize with the visual feedback, and complete a 10-trial practice block with randomized angular deviations of ±5° and ±20°. Participants started each trial by walking to a highlighted start location. Once there, a target (semitransparent cylinder, see figure 1) appeared in the virtual room in one of two randomized locations, 10° to the left or right of the participant’s heading direction, at a distance of 180 cm. Participants were instructed to walk forward in the motion capture area so that their avatar would arrive at the virtual target. Once the participant advanced 30 cm from the start location, the walking trajectory of the virtual body could be veridical (control trial) or systematically deviated toward either the left or the right (by 7.5°, 15°, or 30°). Participants performed 84 trials, including 12 nondeviated control trials, 12 trials for each angular deviation. The trial ended when the participant reached the target distance of 180 cm, even if they missed the target, at which point the target disappeared and participants were asked: “Did the movement shown on the screen correspond to the movement you just performed?,” to which they responded (yes/no) on the gamepad. Subsequently they were asked to report their confidence (“How sure are you of your response?”) with four possible answers (0% guess, 33%, 67%, and 100% certain).

Dependent Variables. The analysis detailed in was followed here with the addition of the confidence ratings. SoA was evaluated using a Yes/No question at the end of each trial; confidence in SoA via a second button press indicating participants’ confidence. Motor performance describes the total angle compensated by the participant considering the endpoint of each of their movement trajectories and measured from the onset of deviation.
Study 2

Procedure. Following the procedure described in, participants walked continuously on a treadmill for the full experimental block. The treadmill-speed was adapted individually (approx. 1 m/s) so that all participants would have a similar stride-time throughout the experiment ($\mu = 1.37$ s; $\sigma = 0.10$). In each trial (144 per condition), participants watched their virtual body perform their own movements either in “real time” (with an intrinsic delay of 75 ms) or with a randomized additional delay (25, 50, 75, 100, 150, 225, 300, 450, 600, 750, 900, 1,050, 1,200, 1,125, 1,275, 1,350 ms; 8 trials per delay, 16 real-time trials). Each trial began with only the fixation-cross and treadmill shown on the screen (2 s). Subsequently, participants received visual feedback of their gait for 3 s, after which they were asked: “Did the movement shown on the screen correspond to the movement you just performed?”. As indicated in figure 1A.

Dependent Variables. Next to the SoA response, we calculated temporal gait characteristics such as stride-time and its coefficient of variance for each temporal delay based on the motion capture data of the heel-markers, as indicated in figure 1A.

Statistical Analysis

SoA and gait characteristics were recorded throughout both studies and processed offline following. All analyses were performed with R, using notably the ggplot2, lme4, lmerTest, and car and effects packages. As described in detail in the supplementary material, logistic mixed-effect regressions were used to analyze SoA responses, linear mixed-effects regressions for all other variables.

Results

Study 1

Sense of Agency. As hypothesized, participants showed high accuracy in the task and judged $97 \pm 6\%$ of un-deviated control trials to be self-generated while judging trials with the largest deviation as non-self-trials ($14 \pm 16\%$). We fitted a logistic mixed-effects regression on SoA judgments, with deviation and group as fixed effects and intercept for participants as random effects. This revealed an effect for Deviation (Wald $\chi^2(1) = 701.195$, $P < .001$) with lower SoA ratings for larger deviations (figure 2A). There was a significant effect for Group (Wald $\chi^2(1) = 5.102$, $P = .024$), driven by a significant interaction between Group and Deviation (Wald $\chi^2(1) = 5.327$, $P = .021$). As predicted this difference was due to higher erroneous self-attribution in deviations with high uncertainty ($15\degree$) in participants with 22q11DS ($\chi^2(1) = 41.9\%$, $\sigma = 30$) compared to participants with 22q11DS ($\chi^2(1) = 41.9\%$, $\sigma = 30$; $P = .011$, Cohen's $d = 0.88$). As discussed below, this difference is not observed for motor corrections.

Confidence Ratings. As expected, confidence ratings revealed a U-shaped confidence curve with higher confidence ratings for self-attributed control trials (no deviation) and trials with the strongest deviation ($30\degree$) that were not self-attributed. The model revealed a main effect of Deviation (for the U-shaped quadratic term, $F(2,2725.46) = 50.95$, $P < .001$), an interaction between first-order accuracy and angular Deviation ($F(2,2724.87) = 119.37$, $P < .001$), and most importantly an interaction between Deviation and Group ($F(2,2725.46) = 7.98$, $P < .001$), see figure 2B. 22q11DS participants reported higher confidence ratings for SoA under uncertainty, for which they also showed less accurate responses. This was driven primarily by...
overconfidence during erroneous SoA judgments in trials with high uncertainty 7.5° ($t(33.074) = 1.97, P = .05$). Thus, 22q11DS participants showed overconfidence when making errors, indicating reduced correspondence between SoA performance and confidence under uncertainty in comparison to the control group.

**Motor Performance.** All participants were able to complete the task by compensating for the introduced angular deviation. This is reflected in the significant main effect of Deviation ($F(1,2734.72) = 2229.28, P < .001$). The differences in SoA are not observed in motor performance, as compensation did not significantly differ between the two groups ($F(1,45.34) = 0.345, P = .671$). There was an interaction between factors group and Deviation ($F(1,2734.72) = 21.024, P < .001$), as control participants compensated slightly more with increasing deviations but this did not reach significance for individual deviations (unpaired $t$-test, $t(28.616) = -1.385, P = .177$). Task completion times neither differed between groups nor interacted with the deviations (see supplementary material).

**Study 2**

**Sense of Agency.** We observed a significant main effect of temporal delay on SoA, resulting in the U-shaped response plot as reported in $^{54}$ (quadratic term: Wald $\chi^2(2) = 537.46, P < .001$). Participants reported high SoA for feedback with the two smallest delays ($\mu = 87 \pm 12\%$ STD for 75 ms) as well as for feedback with delays close to their stride-time ($78 \pm 26\%$ for 1,275 ms) as these latter trials appear re-synchronized with actual walking (figure 3B). In trials with large visuomotor conflicts, participants’ SoA significantly decreased to a minimum for trials with 675 ms delay (40 ± 33%), corresponding to half a step-cycle delay and visuomotor reversal. We observed a main effect of group (Wald $\chi^2(1) = 10.751, P = .001$), as the patient group significantly over-attributed delayed trials. Importantly, there was a significant interaction between factors group and delay group (Wald $\chi^2(2) = 72.643, P < .001$). This was driven by poorer discrimination accuracy, i.e., over-attrtribution of delayed feedback to the self, in the 22q11DS group in trials with large visuomotor conflicts but comparable SoA for synchronous and re-synchronized feedback. Independent $t$-tests show that 22q11DS participants reported higher SoA than control participants in trials with 375–975 ms delay (all $P \leq .038$ using Bonferroni correction for multiple comparisons) but did not differ for trials with 75–225 ms or 1125–1275 ms delay (all $P \geq .490$).

**Motor Performance.** Treadmill-speed was adapted to maintain a similar baseline stride-time for all participants ($F(1,36) = 0.345, P = .561$). As expected from previous experiments, $^{54,55}$ we observed a significant modulation of stride-time based on the temporal delay in the feedback ($F(1,5035) = 7.376, P = .007$), as stride-time slightly decreased with increasing delays. However, unlike in prior studies we did not find a systematic, sinusoidal modulation of the stride-time. The stride-time coefficient of
variation was slightly higher in the 22q11DS population ($F(1,642) = 4.960, P = 0.026, \mu_{22Q11DS} = 5.0\% \pm 2.2, \mu_{control} = 4.7\% \pm 2.0$).

Relation Between Clinical and Behavioral Data

To examine potential relations between the SoA effect and prodromal clinical symptoms, we examined correlations between SIPS Structured Interview for Psychotic Symptoms$^{61,62}$ and SoA ratings for both the temporal and spatial domains (using the highest deviation condition). No significant correlations were found between SIPS positive or negative ratings and SoA judgments for either domain, figure 4.

Similarly, to examine if cognitive functioning as measured by WISC-III-R (or WAIS-III for participants >17 years old) was related to SoA performance we correlated Full-scale, performance and verbal indexes with the SoA ratings in the trials with the highest uncertainty. Once again, no significant correlations between SoA and cognitive functioning scores were found.

Discussion

Our experiments investigated the SoA using an embodied, VR and motion capture paradigm in 22q11DS and control participants. Several novel findings arise from our results. First, these results show that the ability to discriminate self-actions based on sensorimotor information is impaired in participants with 22q11DS. Deficits in SoA were evident in the spatial domain and even more strikingly pronounced in the temporal domain. Second, these differences in SoA are not explained by differences in sensorimotor task performance, suggesting that implicit sensorimotor mechanisms are intact. Finally, participants with 22q11DS demonstrated a poorer performance...
in confidence judgments than control participants in trials with increased uncertainty.

An Altered SoA in 22q11DS

Our results show that both controls and participants with 22q11DS reported diminishing rates of SoA as the visual consequences of their actions diverged from the veridical movements. This effect was robust for both alterations in the spatial and temporal domains, replicating previous work on SoA in healthy populations. Critically, participants with 22q11DS showed reduced ability to discriminate the sensory consequences of their current actions in both the temporal and spatial domains and a tendency to attribute deviated action to themselves (figures 2 and 3). This result extends previous findings from individuals diagnosed with schizophrenia who show deficits in the sense of control over their actions typically coupled with a bias for self-attribution. Further research should address whether differences observed in SOA are also reflected in other self-disorders.

Working with individuals with 22q11DS who have a genetic predisposition for schizophrenia, allowed us to investigate if abnormalities in SoA processing as found in schizophrenia are present in the absence of full blown psychotic symptoms. Our findings show that deficits in SoA are indeed present in 22q11DS individuals with no current diagnosis of schizophrenia or schizoaffective disorder. Thus, the deficits in SoA, found in chronic schizophrenia patients, may precede psychosis. Indeed it has been suggested that SoA deficits can be found in schizophrenotypal populations, however, such correlations are not always found. Importantly, while SoA deficits in psychosis are well established, their relationship to specific symptoms has been less consistent. This suggests that while SoA deficits may be a central feature of psychosis across the schizophrenia spectrum, they do not necessarily manifest in symptoms in a specific fashion across individuals. Our findings extend previous work by showing a novel report of SoA deficits in a genetic model of schizophrenia.

Intact Motor Compensation

Do the erroneous judgments of Agency, found in participants with 22q11DS, stem from deficits in low level sensorimotor processes or alternatively from more high-level judgments of action authorship? Our full body motion paradigm allows us to address this question directly by testing motor correction in addition to SoA judgments. Our results indicate that sensorimotor control did not significantly differ between the groups suggesting that fundamental motor abilities are not likely the cause of erroneous agency judgments. This finding is in line with several accounts in schizophrenia patients who similarly show deficits in explicit judgments of SoA while retaining normal implicit motor compensation mechanisms (but see also).

Over-attribution and Increased Confidence in 22q11DS

Beyond the SoA judgments, we also probed the confidence regarding these judgments. While participants with 22q11DS did not differ from controls in their overall levels of confidence, the 22q11DS group showed lower confidence calibration, that is, their confidence did not follow their performance as well. Deficits in metacognitive capabilities are thought to be a central aspect of schizophrenia, but see, and have been related to reduced neurocognitive capabilities and social functioning. While recent findings have suggested that schizophrenia patients have comparable metacognitive abilities for low level perceptual decisions, the current deficit in metacognition for SoA judgments most likely relates to a meta-executive level in which the sensorimotor conflict induces a conscious and explicit assessment of the authorship of the action. This is in line with the prominent meta-executive deficits in schizophrenia as found for insight into illness and hallucinations.

Is Altered Agentivity a Precursor to Psychosis?

Mounting evidence points to SoA deficits in schizophrenia, giving rise to theoretical suggestions of its role in the ontogenesis of psychosis. Our current findings in a juvenile and nonpsychotic population of 22q11DS participants suggest that deficits in SoA are evident at an early stage. Given the high frequency of psychosis in this population, this indicates that deficits in SoA can be shown prior to the potential rise of psychosis. Although we did not observe a correlation between SIPS ratings and SoA in the current cohort, our findings are in line with several studies showing deficits in SoA in schizophrenotypal or at risk populations. Previous studies have linked 22q11DS to aberrant dopaminergic activity possibly through COMT gene abnormalities, and such anomalous dopaminergic signaling has been linked to psychosis and specifically to metacognitive errors. While our participants did not suffer from psychosis at the time of the study, and may never do so, they showed preliminary deficits in SoA. These deficits in SoA and metacognition of SoA may not cause psychosis directly. However, recent accounts suggest that confusion regarding predictive outcomes of actions may imbalance hierarchical inference and result in overreliance on higher level priors. The idea that sensorimotor conflict processing is related to psychosis symptoms has recently been empirically corroborated using robotic systems such that they induce psychosis-like symptoms including auditory misattributions, presence hallucinations, thought agency, and impact metacognitive processing. Taken together these findings suggest an important role for
abnormal sensorimotor processing in the development of the psychotic state.

Conclusion

In summary, our results indicate that participants with 22q11DS, which is associated with heightened risk of psychosis, show impairments in the SoA over their actions as well as confidence judgments. Thus, our findings link a genetic copy number variant with a propensity for psychosis to a deficit which is distinctive of the psychosis phenotype. Taken together our results suggest that SoA deficits may be a precursor to rather than an outcome of psychosis. SoA may not only be implicated in the development of the psychotic state but could also provide a neurocognitive marker of risk for psychosis.

Supplementary Material

Supplementary material is available at Schizophrenia Bulletin online.

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