Original Investigation

Functional Magnetic Resonance Imaging of Impaired Sensory Prediction in Schizophrenia

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IMPORTANCE Forward models predict the sensory consequences of planned actions and permit discrimination of self- and non–self-elicited sensation; their impairment in schizophrenia is implied by an abnormality in behavioral force-matching and the flawed agency judgments characteristic of positive symptoms, including auditory hallucinations and delusions of control.

OBJECTIVE To assess attenuation of sensory processing by self-action in individuals with schizophrenia and its relation to current symptom severity.

DESIGN, SETTING, AND PARTICIPANTS Functional magnetic resonance imaging data were acquired while medicated individuals with schizophrenia (n = 19) and matched controls (n = 19) performed a factorially designed sensorimotor task in which the occurrence and relative timing of action and sensation were manipulated. The study took place at the neuroimaging research unit at the Institute of Cognitive Neuroscience, University College London, and the Maudsley Hospital.

RESULTS In controls, a region of secondary somatosensory cortex exhibited attenuated activation when sensation and action were synchronous compared with when the former occurred after an unexpected delay or alone. By contrast, reduced attenuation was observed in the schizophrenia group, suggesting that these individuals were unable to predict the sensory consequences of their own actions. Furthermore, failure to attenuate secondary somatosensory cortex processing was predicted by current hallucinatory severity.

CONCLUSIONS AND RELEVANCE Although comparably reduced attenuation has been reported in the verbal domain, this work implies that a more general physiologic deficit underlies positive symptoms of schizophrenia.

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Psychosis has a prevalence of 1% in the population and is a devastating disease that strikes in early adulthood, with only 10% of those affected achieving complete remission.[1,2] Despite a significant investment in pharmacologic and psychosocial treatment during the last 40 years, 20% to 45% of patients experience significant positive symptoms despite optimal antipsychotic treatment.[3,4] The pathophysiologic mechanisms underlying these distressing symptoms remain unclear. Positive symptoms, such as auditory hallucinations and delusions of control, have been postulated to represent a misattribution of self-generated actions as externally generated as a consequence of a dysfunctional self-monitoring mechanism.[5,6] Prediction is fundamental in the physiology of self-monitoring, permitting the sensory consequences of an action to be calculated and used to attenuate the perception related to this sensation.[7-10] The comparison of predicted and actual sensation leads to the sense of agency, whereby concordance signifies that the movement is one's own, whereas discrepancy suggests the movement is externally generated.

In the motor domain, tactile signal attenuation occurs in association with self-generated action. Identical tactile stimuli (eg, tickling or constant forces) are perceived as less intense when self-imposed rather than externally produced.[11,12] For example, when required to subjectively match the sensation of an external force, individuals overestimate the force when reproducing it with their own body directly but crucially not when the force is reproduced indirectly via a torque motor.[13,14] Investigating this phenomenon in individuals with schizophrenia, Shergill et al [14] observed that patients were significantly more accurate than matched controls in their estimations when applying forces directly to themselves, suggesting

a reduction in normal attenuation of self-generated sensation and hence sensory-prediction deficits in these individuals, which may in turn account for their compromised judgment of agency.

In healthy individuals, movement-related tactile attenuation is temporally tuned to match the predicted timing of sensory events.[15,16] When force is produced by right index finger movement and transmitted with varying delay to the left index finger via a torque motor, perceptual attenuation is maximal when tap and force are synchronous and reduced when the force is advanced or delayed relative to the right index finger tap. This reduction has a broad and approximately symmetrical temporal profile of approximately 250 milliseconds, which may be explained by prediction inaccuracy, uncertainty, or an inbuilt safety margin to allow for such prediction error.[16] We have recently found that the blood oxygen level dependence (BOLD) response in the secondary somatosensory cortex (SII) associated with a tactile sensation is attenuated (1) after sensation secondary to a self-initiated action compared with an externally initiated action and (2) when movement and sensation are synchronous compared with asynchronous on account of an added delay.[17] This finding supports the suggestion that the occurrence of movement and its timing relative to sensation modulate the amplitude of the sensory signal as predicted by forward models.

The neuroimaging evidence implying defective corollary discharge in schizophrenia is largely restricted to the verbal domain. Reduction in the N1 event-related potential component is observed during talking and listening compared with listening alone in healthy individuals but not those with schizophrenia.[18] The γ-coherence of electroencephalographic data collected over frontal and temporal lobe regions is greater during talking in healthy individuals but not in those with schizophrenia.[19] Relatedly, healthy individuals but not those with schizophrenia exhibit an attenuation in superior temporal gyrus BOLD activation during inner speech compared with listening.[20] However, given that misjudgment of agency potentially accounts for a wider range of symptoms of schizophrenia, including delusions of control, in which self-generated action is experienced as originating externally, and auditory hallucinations, it is likely that forward-model deficits are not restricted to the neural systems responsible for language processing. Spence et al[21] used positron emission tomography to demonstrate hyperactivation of SII, cerebellum, and anterior cingulate cortex regions during freely selected movements (vs rest) in patients with schizophrenia with passivity symptoms compared with patients without these symptoms and healthy controls. However, although this finding implies sensory-processing abnormality in individuals with passivity problem deficits, this abnormality cannot be ascribed to defective forward-model estimation over compromised sensation per se because the experiment did not investigate sensation in the absence of movement.

We examine these phenomena in individuals with schizophrenia with the aim of explicitly addressing the hypotheses that (1) attenuation of the perceptual BOLD response in SII will be decreased in individuals with schizophrenia compared with control individuals, reflecting impairments in the systems responsible for predicting sensory perception; and (2) the severity of hallucinations, the most prevalent and hence most readily testable symptom potentially attributable to impaired agency judgment, will be associated with the severity of related BOLD impairments in the schizophrenia group.

Methods

Participants

Nineteen dextral individuals who satisfied the *DSM-IV*[22] criteria for schizophrenia (mean [SD] age, 35.7 [7.9] years; 4 women) and 19 dextral controls (mean [SD] age, 34.2 [8.2] years; 6 women) and were group matched for age, sex, and premorbid IQ, as assessed by the National Adult Reading Test,[23] were recruited to take part in this functional magnetic resonance imaging (fMRI) study. Ethical approval was provided by the South London and Maudsley Research and Ethics Committee. All participants provided informed written consent and were given a monetary inconvenience allowance for participation in the study.

Patients were excluded if they presented evidence of a comorbid Axis I diagnosis, significant medical illness, or an IQ of less than 85. Symptom severity and classification were assessed in the schizophrenia group using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.[24] They scored a mean (SD) of 19.08 (6.16) on the positive subscale, including 3.20 (1.61) for hallucinations; 13.25 (3.84) on the negative subscale; and 35.00 (6.56) on the general psychopathology subscale.

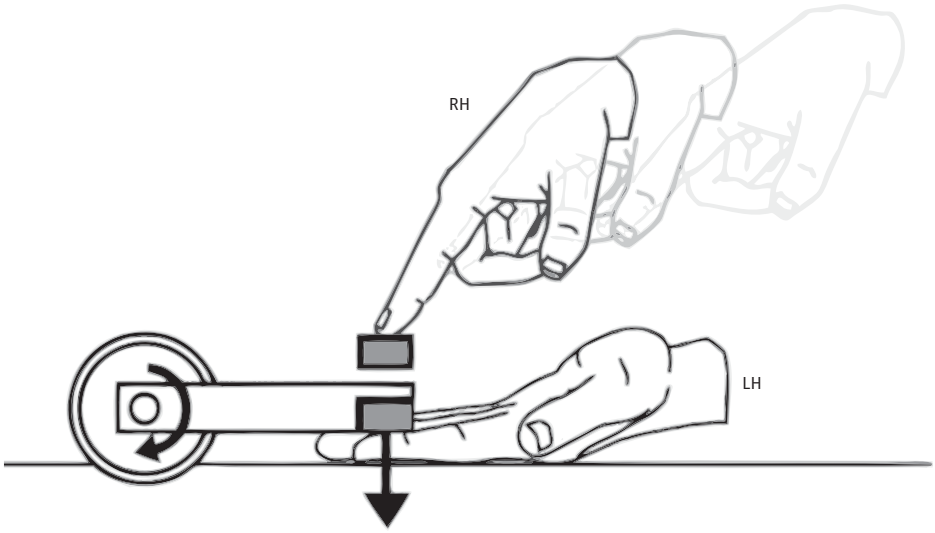
All individuals with schizophrenia were medicated at the time of the study. Seventeen of these patients were prescribed atypical antipsychotic medications (amisulpride [n = 1], clozapine [n = 2], olanzapine [n = 4], quetiapine fumarate [n = 2], risperidone [n = 8]), and 2 were prescribed typical antipsychotic medications (chlorpromazine [n = 1] and flupenthixol depot injection [n = 1]) at time of participation. The chlorpromazine equivalent of antipsychotic medication dosage was calculated according to published conversion tables[25] and observed to be a mean (SD) of 197.3 (133.7) mg/d of chlorpromazine.

Healthy volunteers were recruited by local poster advertisement. Respondents were excluded from the study if they reported a personal history of psychiatric or neurologic illness, exhibited a major current physical illness or an IQ less than 85, had a recent history of illicit substance use, or had a history of psychotic illness in a first-degree relative.

Experimental Procedure

Participants performed a sensorimotor task that comprised two 14-minute sessions, containing a total of 200 randomly ordered experimental trials split equally between the experimental conditions and 60 randomly interpolated null trials. The experimental apparatus is depicted in **Figure 1** and force measured through the use of 2 pressure sensors mounted one above the other.[16] The upper sensor was fixed in space, and the lower was mounted on the end of a lever that was attached to a small torque motor. This apparatus permitted a tap (by the right in-

Figure 1. The Experimental Setup



Force is applied to an upper sensor by the index finger on the right hand (RH) and transmitted to the index finger on the left hand (LH) via a sensor mounted on a lever driven by a torque motor. Computerized control of this system manipulated the occurrence and timing of left index finger sensations in both the absence and presence of right index finger movements.

dex finger) on the upper sensor to be transmitted synchronously, asynchronously with a 500-millisecond delay, or not at all to the left index finger. Moreover, the tactile stimulus on the left finger could also be presented in the absence of a right finger tap. The experiment was arranged as 8 experimental conditions in a 2 × 2 × 2 factorial design. The factors were (1) the presence or absence of self-generated movement, that is, the right finger tap on the upper sensor (M1/M0); (2) the presence or absence of a tactile stimulus delivered to the left finger (S1/S0); and (3) the presence or absence of a 500-millisecond delay between the application of the right finger tap and its transmission to the left finger (D1/D0). Thus, the 8 experimental conditions were self-produced tactile stimuli (M1S1), externally produced tactile stimuli (M0S1), and self-produced movement without tactile stimuli (M1S0) and rest (M0S0)—each with and without a 500-millisecond delay (M1S1D0, M1S1D1, M1S0D0, M1S0D1, M0S1D0, M0S1D1, M0S0D0, and M0S0D1). The use of a factorial design necessitated the inclusion of delay trials for each of the 4 primary conditions, although there was no real difference among the trials when the delay coincided with an absence of tactile stimuli. Each trial lasted 6.5 seconds and consisted of a visual cue that indicated tap or do not tap (1 second), a countdown (1.5 seconds), a response period (1 second), and a rest period (3 seconds). Participants viewed a screen onto which visual stimuli were projected through appropriately aligned mirrors mounted on the scanner head coil.

MRI Data Acquisition

BOLD functional images were acquired on a 3-T system (Signa Excite; General Electric) with an 8-channel head coil using an echo planar imaging sequence with the following parameters: repetition time, 2600 milliseconds; echo time, 30 milliseconds; and flip angle, 90°. In each of two 14-minute sessions, 166 volumes that comprised 40 descending, sequentially ordered 2-mm axial slices (with a 1.6-mm gap between slices) and an in-plane resolution of 3 × 3 mm were acquired.

fMRI Data Preprocessing and Analysis

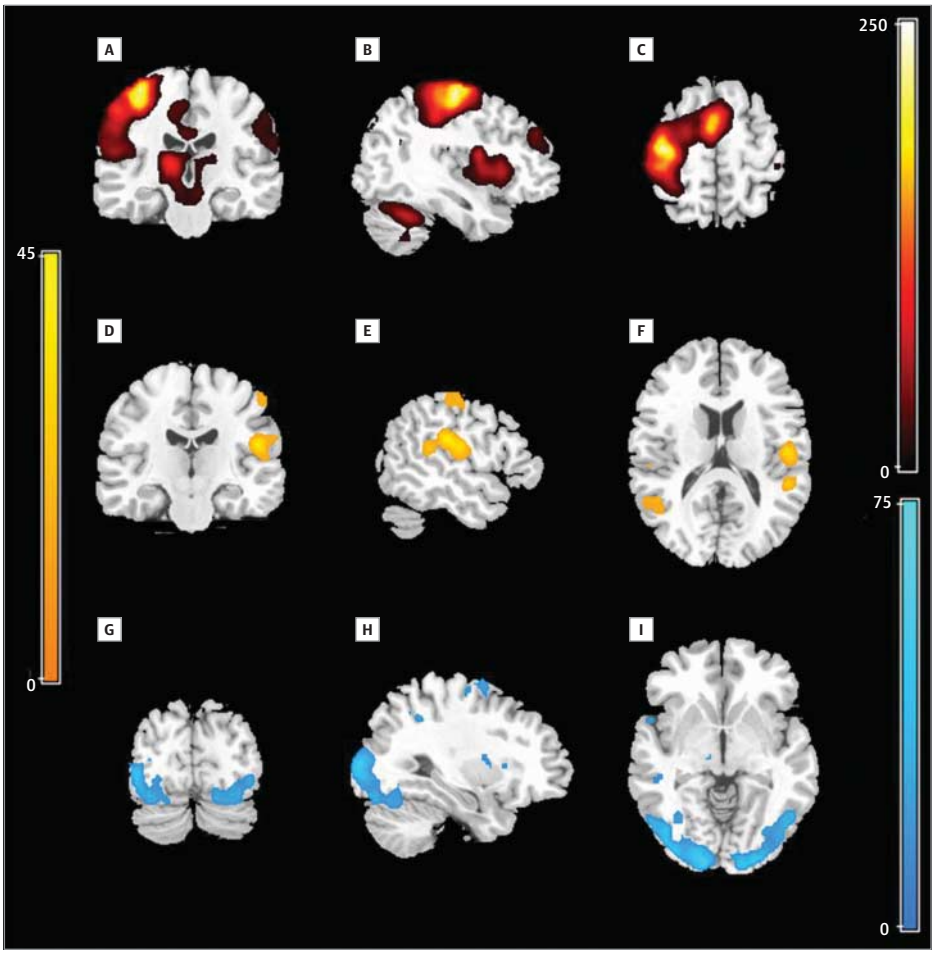
The fMRI data were preprocessed using SPM5 statistical software (Wellcome Department of Imaging Neuroscience, University of London). Data were realigned to the first image, normalized to a standard template of the Montreal Neurological Institute brain, and smoothed using an 8-mm full-width at half-maximum gaussian kernel.

First-level event-related general linear models were constructed for each participant. These models included a regressor that predicted the BOLD response to each condition by convolving a vector of Δ functions for the onset of the response instruction for that condition with the canonical hemodynamic response function. The first and second derivatives of these time courses were also calculated and included as further regressors for each condition. Effects of head motion were minimized by the inclusion of 6 realignment parameter vectors as regressors of no interest. First-level contrast images were calculated for the canonical responses to each of the 8 experimental conditions, which were entered into a second-level random-effects analysis of variance (ANOVA) model to assess within-subject effects of motion, sensation and delay, and the between-subject effects of group. Significance was ascribed according to a cluster-level criterion (family-wise error-corrected $P < .05$) based on the spatial extent and number of suprathreshold voxels (uncorrected $P < .001$).[26]

Region of Interest Analysis of Effects of Concomitant Motor Act and Delay on Sensory Perception

In addition to the whole-brain analysis, a region of interest (ROI) approach was adopted to investigate task effects in SI, SII, and cerebellum. For these regions, mean data for a sphere of a 6-mm radius were extracted and activity in these spheres assessed using the same ANOVA models as in whole-head mass univariate analysis. The center of each ROI location was determined using previously published forward-model effects for SII (x = 42, y = −24, z = 18) and cerebellum (x = 22, y = −58, z = −22) according to Blakemore et al.[11] For SI, the ROI location

Figure 2. Significant Main Effects of Motion, Sensation, and Group



A-C, Motor effects according to the red F-value scale. D-F, Sensation effects according to the orange F-value scale. G-I, Group effects according to the blue F-value scale. Images are overlaid on a standard T1-weighted magnetic resonance image and shown according to the neurologic convention.

was determined using the index finger locus identified in relation to somatotopic organization of SI (x = 49, y = −19, z = 45).[27] The SI and SII analyses were limited to gray matter voxels within these using a binarized template mask with the aim of enhancing sensitivity for neuronally derived signals. Repeated-measures ANOVA was used to assess within-subject effects of movement, sensation, and delay on contrast estimates in the 3 ROIs.

To investigate effects of movement and delay on somatosensory activation more explicitly, we conducted a further ROI analysis of the 3 most pertinent experimental conditions: M1S1D0 (force transmitted synchronously), M1S1D1 (force transmitted with delay), and M0S1D0 (force transmitted without movement). To ascertain whether movement significantly reduced concomitant somatosensory responses, we compared mean contrast estimates within these regions for the M1S1D0 and M0S1D0 conditions using a paired-sample *t* test for each region. To ascertain whether the introduction of delay modulated the predicted somatosensory attenuation, comparisons between the contrast estimates for the M1S1D0 and M1S1D1 conditions were judged using further paired-sample *t* tests.

Association With Psychiatric Symptoms

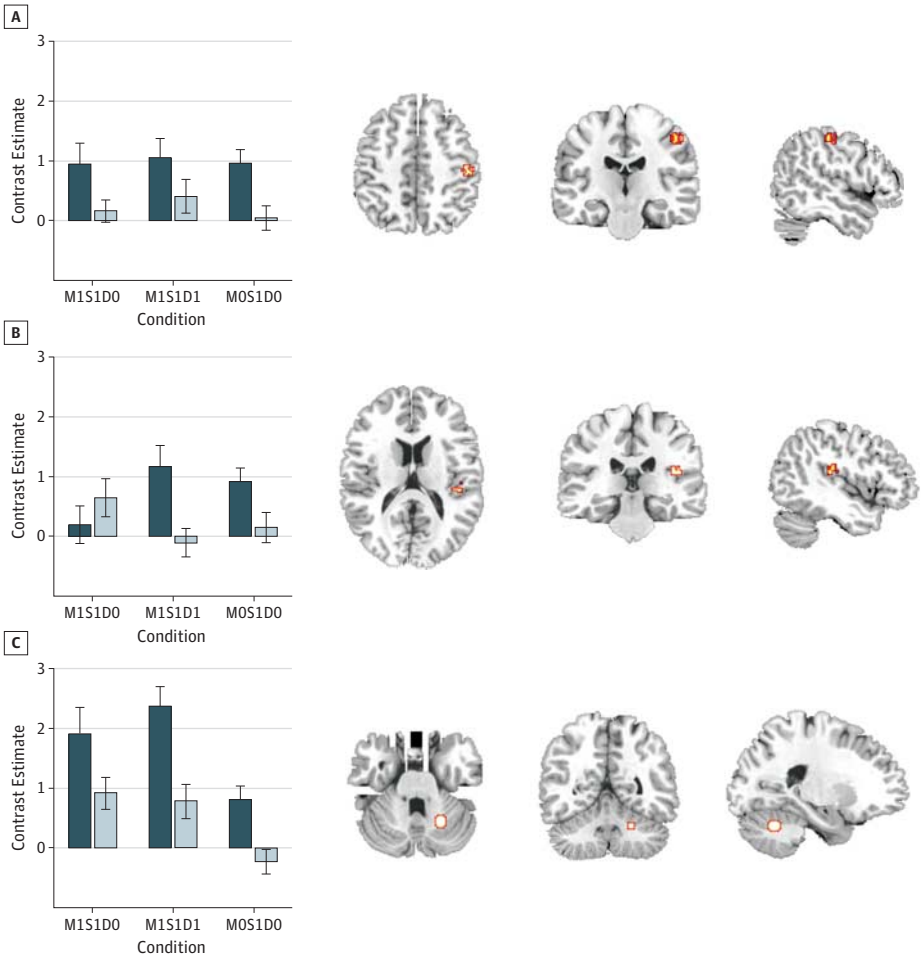
Movement-related sensory attenuation was calculated by subtracting the mean contrast estimate for the SII ROI for M1S1D0 trials from that for M0S1D0 trials, given previous observations that sensory attenuation is maximal during coincident movement.[16] The association between attenuation and PANSS hallucination score was then evaluated using the Spearman rank test. Focus on hallucinations rather than delusions of control reflects the methodologic advantage associated with their greater prevalence in the schizophrenic population (auditory hallucinations, 70%[28]; delusions of control, 25%[29]); however, we propose forward-model deficits as fundamental to symptoms that involve impaired agency judgments more generally. Effects of age, sex, and chlorpromazine equivalent dosage on this association were not covaried out because these variables were observed to be nonsignificantly related to sensory attenuation on the basis of equivalent tests. Further investigation of medication effects on BOLD activation during the experiment is presented in eAppendix 1 in the Supplement.

Results

Secondary Somatosensory Cortex

Significant clusters of activation were observed in bilateral SII and right SI for the main effect of sensation. This and all other significant whole-brain effects are presented in **Figure 2**; eTable

Figure 3. Condition-Specific Task Estimates and Region of Interest Location



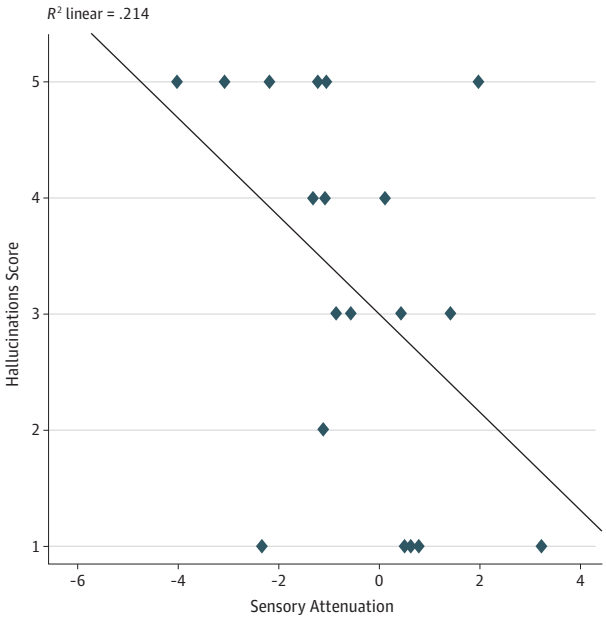
A, Primary somatosensory cortex; B, secondary somatosensory cortex; C, cerebellum. Error bars indicate SEM. M1S1D0 indicates force transmitted synchronously; M1S1D1, force transmitted with delay; and M0S1D0, force transmitted without movement.

1 in the Supplement presents statistics that relate to their gray matter foci. The ROI analyses confirmed the significant main effect of sensation in SII ($F_{1,37}$ = 12.838, P = .001). Post hoc t tests on the ROI data revealed that there was greater activation overall for trials that included tactile sensation compared with those with no sensation (sensation β: 0.44 [0.15]; nonsensation β: 0.01 [0.13]; T_{37} = 3.582, P = .001). Significant movement × delay × group ($F_{1,37}$ = 7.436, P = .01) and sensation × delay ($F_{1,37}$ = 6.198, P = .02) interactions were also observed in the SII ROI. Importantly, a significant movement × sensation × delay × group interaction ($F_{1,37}$ = 4.873, P = .03) was also observed in this region. This effect is plausibly accountable to varying patterns of abnormal processing (see eAppendix 2 and eTable 2 in the Supplement). Healthy individuals demonstrated significant attenuation of SII activation when movement and sensation occurred synchronously compared with sensation alone (M1S1D0 vs M0S1D0: T_{18} = 2.415, P = .03) and also compared with asynchronous movement and sensation (M1S1D0 vs M1S1D1: T_{18} = 3.745, P = .001); however, individuals with schizophrenia exhibited nonsignificant differences between these conditions. These results are presented in **Figure 3**. No other main or interaction effects were significant in SII. In the schizophrenia group, the degree of movement-related sensory attenuation was significantly negatively correlated with the PANSS hallucination score (ρ = −0.477, P = .04; **Figure 4**).

Cerebellum

Self-generated movement produced significant clusters of activation in the right anterior cerebellum, left primary motor cortex, and bilateral supplementary motor area (Figure 2 and eTable 1 in the Supplement). The ROI analyses also demonstrated a significant main effect of group for cerebellar activation ($F_{1,37}$ = 18.190, P < .001). The t tests on the cerebellar ROI mean contrast estimates across conditions demonstrated that healthy individuals exhibited greater activation than patients (control β: 1.39 [0.22]; patient β: 0.30 [0.12]; T_{37} = 4.27, P < .001). Significant main effects of self-generated movement ($F_{1,37}$ = 31.828, P < .001) and sensation ($F_{1,37}$ = 4.98, P = .03) were also observed in the cerebellar ROI. Post hoc t tests demonstrated that activity here was greater in movement than nonmovement conditions (movement β: 1.45 [0.28]; nonmovement β: 0.23 [0.16]; T_{37} = 5.63, P < .001) and in sensation than nonsensation conditions (sensation β: 0.96 [0.18]; nonsensa-

Figure 4. Sensory Attenuation in Secondary Somatosensory Cortex and Current Hallucinatory Severity as Measured Using the Positive and Negative Syndrome Scale[24]



Individual-specific data for the schizophrenia group and the associated best-fit line are shown (R^2 linear = .214).

tion β: 0.72 [0.15]; T_{37} = 2.26, P = .03). The ROI activation was greater when movement occurred with both synchronous and asynchronous sensation compared with when sensation was experienced without movement for both healthy individuals (M1S1D0 vs M0S1D0: T_{18} = 3.13, P = .006; M1S1D1 vs M0S1D0: T_{18} = 6.42, P < .001) and individuals with schizophrenia (M1S1D0 vs M0S1D0: T_{18} = 3.47, P = .003; M1S1D1 vs M0S1D0: T_{18} = 2.90, P = .01; Figure 3). No other main or interaction effects were significant in the cerebellum.

Primary Somatosensory Cortex

In addition to the whole-brain main effect of sensation observed in SI, significant main effects of self-generated movement ($F_{1,37}$ = 4.58, P = .04), sensation ($F_{1,37}$ = 12.52, P = .001), and delay ($F_{1,37}$ = 4. 18, P = .04) were observed in the SI ROI. The t tests revealed that activation was greater during movement compared with nonmovement trials (movement β: 0.51 [0.18]; nonmovement β: 0.22 [0.14]; T_{37} = 2.16, P = .04), sensation compared with nonsensation trials (sensation β: 0.54 [0.15]; nonmovement β: 0.19 [0.16]; T_{37} = 3.53, P = .001), and delay compared with nondelay trials (delay β: 0.48 [0.16]; nondelay β: 0.26 [0.15]; T_{37} = 2.22, P = .03). A significant main effect of group ($F_{1,37}$ = 5.56, P = .02) was also observed in the SI ROI, with greater activation in healthy individuals compared with individuals with schizophrenia (control β: 0.70 [0.24]; patient β: 0.04 [0.14]; T_{37} = 2.36, P = .02). Nonsignificant differences in SI activation were observed in both groups among the 3 conditions of interest (Figure 3). No other main or interaction effects were significant in SI.

Discussion

Evidence indicates that the engineering-based models that describe forward or predictive models in motor control are useful in describing sensorimotor learning[30,31] and putative deficits can be linked to behavioral changes evident in schizophrenia.[14] However, little work has tested the neural basis for these putative deficits using fMRI,[20,32] although there are positive findings from electrophysiology,[18,19,33] which has less regional specificity. This article reveals the physiologic mechanism underlying this defective sensorimotor prediction in schizophrenia. First, patients with schizophrenia do not demonstrate attenuation in somatosensory cortical activation in association with self-generated movement, in contrast to healthy individuals who exhibited significant reductions in SII activation during synchronous self-generated movement compared with when sensation occurs in the absence of self-movement or when sensation is delayed relative to self-movement. Second, this lack of attenuation in patients with schizophrenia is predicted by the severity of their hallucinatory experiences.

These findings provide a cerebral basis for the increasing body of behavioral evidence that suggests that impaired motor prediction leads to a set of symptoms of schizophrenia explicable by a fundamental misjudgment of agency.[14,34-37] Comorbidity of these symptoms[38] feasibly suggests a shared pathophysiologic mechanism; however, this model does not address complex phenomenologic features of these symptoms.[39,40] Nevertheless, our earlier findings have been replicated by Teufel et al,[35] who demonstrated that healthy individuals overestimate force when directly applying it to their finger compared with when applying it to a slider. Limiting their study to healthy individuals, with the rationale that individuals with psychotic illness merely occupy an extreme position on a normally distributed population-wide phenotypic continuum, they reported an inverse association between force estimation and delusional ideation. Since this and our current results were not confounded by medication effects, it is unlikely that antipsychotic medication accounts for the predictive impairments observed in individuals with schizophrenia.

Although forward models are an integral part of the process of judging agency, by comparing the predicted sensory state specified by a self-generated movement and the actual sensory state, several additional processes are necessary to facilitate flexible control, online correction, and movement coordination.[41] In a study in which individuals performed arm-pointing movements and received visual feedback via a virtual-reality relay, Synofzik et al[37] observed that individuals with schizophrenia were less able to detect manipulation in visual feedback and that severity of delusions of influence predicted this performance impairment. The former implies a preference for visual over kinesthetic feedback in schizophrenia on account of kinesthetic inaccuracy. Similarly, during smooth-pursuit eye movements, which require dissociation of self-induced movement from both object and background movement, individuals with schizophrenia were less accurate at

parsing environmental movement and self-induced image movement (attributing their own movements to the environment) with those experiencing delusions of control particularly impaired in this regard.[34] The extent to which sensory feedback can assist forward-model updating depends on behavioral context and movement specifics. Nevertheless, future research should aim to dissociate impairments attributable to aberrant updating of models by sensory feedback from those caused by inaccurate prediction of sensation; electroencephalography represents a particularly apposite method for such work.

Impaired sensorimotor prediction has been previously observed during speech-based tasks using neuroimaging[18-20]; however, our findings suggest that the effects of impaired prediction are evident across multiple functional domains. The association between severity of hallucinatory experience and finger movement–related forward-model phenomena reveals a cross-modal aspect to deficits in sensory prediction, although it is emphasized that this association should not necessarily be considered specific to hallucinations but rather indicative of a fundamental aberrance with multiple potential cognitive sequelae. A parsimonious explanation of the verbal and motor impairments that have now been observed is that they are downstream effects of a generalized forward-model estimation inaccuracy. The neural source of this impairment is not yet known, but a critical role for the cerebellum is intimated by findings that developmental damage and transcranial-magnetic stimulation virtual lesions produce behavioral deficits suggestive of a compromised ability to predict the sensory consequences of action.[42-44] Blakemore et al[11] observed correlates of tactile attenuation in the right cerebellum in healthy controls, when movement accompanied sensation compared with when sensation occurred alone, implying that cerebellar activity mirrors the pattern of response in the sensory cortex. Our current findings of significant effects of movement and sensation in the cerebellum suggest that the cerebellum is adequately performing its comparator function across both study groups. However, a main effect of group was observed for cerebellar activity across conditions. It is possible that the between-group differences in attenuation observed in SII are the result of diminished cerebellar activity in the patient group.

In summary, this work presents a physiologic basis for the predictive deficits previously reported in schizophrenia using the force-match task.[14,35] Unlike healthy individuals, individuals with schizophrenia do not attenuate predictable sensory signals, suggesting that they are unable to predict the sensory consequences of their own actions. Although comparably reduced attenuation has been previously reported in the verbal domain, this work finds for the first time, to our knowledge, that this physiologic deficit is exhibited more generally. This discovery opens the way for examination of a tripartite cognitive, neurophysiologic, and psychopharmacologic investigation to examine the therapeutic potential of this approach to explain the mechanisms underlying psychotic illness.

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Acquisition of data: Shergill, Joyce.
Analysis and interpretation of data: Shergill, White, Joyce, Frith.
Drafting of the manuscript: Shergill, White.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Shergill, White, Joyce, Frith.
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