In and out of control: brain mechanisms linking fluency of action selection to self-agency in patients with schizophrenia

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Abstract

Sense of agency refers to the feeling of control over one's actions, and their consequences. It involves both predictive processes linked to action control, and retrospective "sense-making" causal inferences. Schizophrenia has been associated with impaired predictive processing, but the underlying mechanisms that impair patients' sense of agency remain unclear. We introduce a new, "prospective" aspect of agency and show that subliminally priming an action not only influences response times, but also influences reported sense of agency over subsequent action outcomes. This effect of priming was associated with altered connectivity between frontal areas and the angular gyrus. The effects on response times and on frontal action selection mechanisms were similar in patients with schizophrenia and in healthy volunteers. However, patients showed no effects of priming on sense of agency, no priming-related activation of angular gyrus, and no priming-related changes in fronto-parietal connectivity. We suggest angular gyrus activation reflects the experiences of agency, or non-agency, in part by processing action selection signals generated in the frontal lobes. The altered action awareness that characterises schizophrenia may be due to impaired communication between these areas.

Keywords: selection fluency; agency; angular gyrus; dorso-lateral prefrontal cortex; schizophrenia.

Introduction

The sense of agency refers to the feeling that one controls one's own actions, and, through them, events in the external world. It is considered a key component for understanding the self in health and disease.

Disordered sense of agency is a characteristic feature of psychotic syndromes (Frith, 1992; Nelson *et al*., 2013a, 2013b). The common feature of these experiences – succinctly captured by the term *Ichstörungen* ("self-disturbance") coined by the early 20th century Heidelberg School of psychiatry in Germany (Jaspers, 1913; Gruhle, 1929; Spitzer, 1988) – is a loss or disturbance of experienced control over one's own actions, emotions and cognitions (Jeannerod, 2009; Heinz *et al*., 2012; Vosgerau and Voss, 2013). Schneider (1942, 1958) argued that these self-disturbances were "highly specific for schizophrenia" and classified them along with some types of delusions or hallucinations, as "first rank symptoms" (FRS). There is still a wide consensus that such disturbances of the "mineness of experience" constitute a key feature of psychosis, and a fundamental alteration of core aspects of the self (Sass and Parnas, 2003; Mishara et al., 2014). Nevertheless, the pathognomonic nature of FRS has been questioned by some recent studies (Peralta et al., 1999; Ihara et al., 2009) and the American Psychiatric Association (APA) has removed reference to FRS from the new version of the DSM-5 (Tandon et al., 2013; Heinz, Voss et al., 2016) – perhaps because of the difficulties of relating alterations of sense of agency to quantitative measurements and to specific neurobiological mechanisms. However, a rigorous scientific account of sense of agency could have genuine clinical value, since disturbances of the "basic self", such as altered awareness of action, are a phenotypic trait marker of schizophrenia. In principle, therefore, detailed assessment of sense of agency could be used to identify prodromal stages of the disease (e.g., Nelson et al., 2009; Hauser et al., 2010).

Sense of agency involves an interplay between predictions based on internal processing of current action control signals, and retrospective inferences, based on sensory feedback, about the causes of events (Haggard and Tsakiris, 2009; Haggard and Chambon, 2012; Moore and Fletcher, 2012; Synofzik, Voss, *et al.*, 2013). Accordingly, disturbances of self-agency in schizophrenia have been linked to deficits in internal monitoring processes in general (e.g. Malenka et al., 1982; Franck et al., 2001; Fourneret et al., 2002; Lindner et al., 2005) and, more specifically, to a failure to predict future events, such as one's own impending actions and their consequences (Frith et al., 200; Blakemore et al., 2002; Shergill et al., 2005). Individuals suffering from schizophrenia seem to compensate for such prediction deficits by more strongly weighting afferent information about action outcomes, reflecting an increased reliance on retrospective cues to agency (Voss *et al*., 2010; Synofzik et al., 2010; Chambon *et al*., 2011, Werner et al., 2014).

This interplay between prospective and retrospective information has often been interpreted using comparator models of motor control (e.g., Blakemore, Wolpert, et al., 2002). In these models, an efference copy of motor commands is sent to an internal predictor, that predicts the likely outcome of the motor command. These predictions could include both the movements or states of one's own body, and also the external outcomes of one's own actions. A comparator node then compares afferent inputs to these predictions, generating a prediction error. It has been suggested that sense of agency is felt with respect to an event when predictions and afferent signals cancel, leaving no prediction error at the output of the comparator. Clearly, these models contain at least two key signals relevant to sense of agency. The first of these is the efference copy itself, which signals that a specific action will occur. The second is the re-afference that an action or its outcome has actually occurred. The efferent signal necessarily precedes the action, and can therefore be called prospective, while the re-afferent signal is necessarily delayed by feedback conduction delays, and is therefore

retrospective. Thus, comparator models compute sense of agency by fusing both prospective and retrospective signals. Importantly, the comparator itself cannot compute until re-afferent signals are available, so the final output of the model is, in this sense, always retrospective.

Recent studies have focussed on the retrospective aspects of the comparator model. For example, cancelling sensory information about action outcomes against the predictions of an internal model based on efference copy allows events to be attributed to one's own action or not (Timm *et al*., 2014). Models that focus on the link between actions and their outcomes, such as the comparator model, can be taken as emphasising a retrospective view of sense of agency. In contrast, models that focus on earlier stages of the action processing chain, such as action selection, emphasise a prospective view. On the retrospective view, agency is strongly dependent on how predictable the effect of action is, and hence on minimizing prediction error between actual and predicted effect (e.g., Blakemore, Wolpert, et al., 2002). In contrast, the prospective view does not make any claim about predictability of effect, and does not require the actual effect of action to be known for the computation of sense of control to begin. Rather, the prospective view assumes that signals arising during selection and prior to execution can influence sense of control, in addition to re-afferent or predicted information about action outcomes (e.g., Wenke et al., 2010). Several studies have suggested that signals experienced at the critical moment of choice are relevant to the experience of control (e.g., Wenke et al., 2010; Chambon et al., 2013; Stenner et al., 2014; Sidarus et al., 2014). The contribution of these early signals does however not rule out a role for efference-based internal models, neither does it imply that action effects are irrelevant to sense of agency. Normally, both prospective and retrospective information relevant to agency are available. A robust and reliable sense of agency presumably requires optimally combining both prospective and retrospective components.

Here we describe a specific *prospective* process that contributes to sense of agency,

namely the process of selecting between action alternatives. Since action selection necessarily precedes dispatch of the efferent motor command, this component of agency would clearly be prospective. We used fMRI to identify the brain circuits that process the action selection signal and investigate its influence on sense of agency. In a group of patients diagnosed with schizophrenia, we demonstrate for the first time how this mechanism is altered in psychosis.

We used subliminal priming to selectively influence action selection. Subliminally priming people regarding which of two actions to make causes changes in response time (Eimer and Schlaghecken, 2003). Primes can facilitate or impair selection of the appropriate action in response to a subsequent cue, or can bias free selection. Interestingly, compatible primes also induce a stronger feeling of control over an external outcome of action (Wenke *et al*., 2010), compared to incompatible primes. Crucially, this effect of subliminal priming on sense of control occurs even when there is no doubt about the authorship of the action and of the resulting outcome, or even when the prime is unrelated to the outcome of the action (Chambon and Haggard, 2012; Chambon *et al*., 2013). This suggests that the processes of action selection contribute to sense of agency. Since action selection necessarily precedes action execution, this would constitute a *prospective* component of sense of agency.

Sixteen healthy adults and sixteen individuals with schizophrenia participated in our study. Different response types were used to disentangle the effect of action selection processing (e.g., fluent vs. dysfluent) from the effect of the generative source of action (e.g., external vs. internal) (e.g., Marcel, 2003). While it has been previously shown that action selection processes make a contribution to subjective sense of control (e.g., Wenke et al., 2010), it remains unclear whether different sources of action generation could also contribute. Thus, in the following experiment, subliminal arrow primes were used to influence either cued-choice or free-choice keypress responses to a subsequent left, right or double-headed arrow cue. Participants' responses caused a colour to appear, after a variable delay.

Participants then judged how much control they felt over this visual outcome of their action. Crucially, the colour shown was not related to the prime alone. Rather, one set of colours was shown when prime and cue were compatible with the subsequent target, and another set when they were incompatible. Likewise, in free-choice conditions, primes could be compatible or incompatible with the hand used to respond. Thus, our primes manipulated the fluency of action selection, allowing us to investigate the prospective contribution of selection processes to sense of agency, in both healthy volunteers and in psychotic patients.

<< Insert Fig. 1 about here >>

We show that action priming had similar influences on prefrontal action selection processing in both volunteers and patients. Action priming further influenced sense of agency via connectivity with the angular gyrus, but this mechanism was absent in the psychotic patients. This result suggests that altered action awareness in schizophrenia could arise from failure to prospectively experience internal signals of selection fluency at the critical moment of choice, due to impaired interplay between frontal action-selection and parietal monitoring mechanisms. Instead, we observed a stronger reliance on retrospective cues such as the interval between an action and its effect, which could reflect a compensatory mechanism.

Materials and Methods

Participants

Sixteen right-handed non-psychiatric healthy volunteers (3 females and 13 males aged 23–43 years), and sixteen right-handed individuals with schizophrenia (5 females and 11 males aged 24–49 years), with normal or corrected-to-normal vision, were recruited to participate in the study. Patients and healthy volunteers were matched for handedness, age, and sex (Table 1). In patients, negative and positive symptoms were evaluated with the SANS (Scale for the Assessment of Negative symptoms, mean: 23.4, SD: 14) (Andreasen, 1983) and the SAPS (Scale for the Assessment of Positive symptoms, mean: 21.6, SD: 19.9) (Andreasen, 1984). For each patient, a "ego-disturbance" score was also computed by summing the following subscores from the SAPS: delusions of mind reading, thought broadcasting, thought insertion, thought withdrawal, somatic delusions, delusions of being controlled, ideas and delusions of reference. These items have been shown to constitute fundamental components of passivity experience, whose common feature is a perceived loss or disturbance of control over one's own actions and cognitions (Jeannerod, 2009; Heinz *et al*., 2012). Of the 16 schizophrenic patients, two were excluded because of: claustrophobia (1; the patient could not complete the test), or excessive motion (1; more than one translational displacement of 3 mm or greater). Of the 16 comparison participants, two were also excluded because of: excessive motion (1; more than one translational displacement of 3 mm or greater), or high sensitivity to subliminal primes (1; see Results, prime-visibility test). All participants provided written informed consent prior to the experiment according to the Declaration of Helsinki, and were all paid €30 for their participation. The study was approved by the local ethics review board at the Charité University Hospital, Berlin, Germany.

<< Insert Table 1 about here >>

Experimental design and procedure

The visual display was presented on a screen (display mode= 800 × 600 × 32, 60 Hz) positioned at the front of the magnet bore. Subjects lay supine in the scanner and viewed the display on a mirror positioned above them. The experiment was programmed and stimulations were delivered using the software Presentation (Neurobehavioral Systems, Albany, California, http://www.neurobs.com).

Primes consisted of grey left- or right-pointing arrows followed by metacontrast masks of the same luminance (see **Fig. 1**). The metacontrast masks also consisted of arrows that either pointed to the left or the right (in cued-choice trials), or in both directions simultaneously (in free-choice trials). Prime and mask stimuli could appear randomly above or below fixation to enhance the masking effect (Vorberg *et al*., 2003). All stimuli appeared on a grey background.

Participants made left or right keypress actions on each trial using the index fingers of their left and right hands, and made control ratings using all fingers of each hand, with the exception of thumbs. To respond to targets as to make their control judgments, participants used two 4-buttons response-boxes placed in their left and right hands.

Examples of each mask stimulus (left-, right-, and double-pointing arrows) were presented during experimental instruction so that participants would become acquainted with the target stimuli. No reference was made to the existence or appearance of the primes. The participants' task was to monitor, and then judge how much control they had over colour-effect stimuli that followed left and right keypress actions.

Cued and free-choice trials were randomly intermixed within blocks. On cued-choice trials, participants pressed the left and right keys in response to left- and right-pointing arrow

mask cues. On free-choice trials they saw a double-pointing arrow mask, and could respond as they wished. They were encouraged to avoid fixed response schedules (e.g., alternating between responses), and approximately balance response frequencies. In both cued and free trials, left or right-pointing subliminal arrows appeared before the cue (see **Fig. 1)**.

In half of the cued trials at random, the prime and the mask/target (and therefore also the manual response, assuming that participants responded correctly) were *compatible***,** while on the remaining trials they were *incompatible*. On compatible trials, the direction of the prime corresponded to the direction of the mask/target, and hence signalled the same response. On incompatible trials, prime and mask/target pointed in different directions. On free trials, compatibility was defined online after the subject had responded, because the mask did not unambiguously signal a "correct" response. Responses were classified as prime-compatible when participants "freely" choose the response suggested by the prime, and otherwise as incompatible.

A coloured circle appeared 100, 400 or 700 ms after each response. This randomized jitter produced strong variations in the perceived sense of control over the colour (Haggard *et al*., 2002; Wenke *et al*., 2010). The delay was orthogonal to prime-response compatibility manipulations.

Four colours were shown for prime-compatible responses (two for each hand), and four different colours for prime-incompatible responses. Colours were equally predictable across compatible and incompatible priming conditions. Specifically, the colour was independent of the direction indicated by both the subliminal prime and the target arrow (and hence independent of the keypress made by the subject), but depended only on the compatibility relation between the prime and the subsequent target. We reasoned that making the colour vary with the prime-target relation should facilitate participants in distinguishing between the different subjective experiences associated with fluent or dysfluent prime-

induced action selection, and hence should provide an additional basis for perceptual labelling and rating of control in these conditions (see Wenke et al., 2010 for a similar procedure).

Participants reported how much control they felt they had over the colour effect by using a scale ranging from 1 (no control) to 8 (complete control).

Timeline of experimental trials

Each trial began with a central fixation cross which remained visible until the colour-effect stimulus appeared (Fig. 1). Primes were presented for 16.67 ms (i.e., one frame), followed by a mask after an SOA (Stimulus Onset Asynchrony) of 33.3 ms (i.e., two frames). The masks served as cues for motor responses. Mask/cue duration was 250 ms. The response window was set to 1200 ms. If participants failed to respond within this time window, or made an incorrect response to the mask/target, they saw a black X instead of a coloured circle. The coloured patches showing action effects remained on the screen for 300 ms. After a jittered delay (grey background) varying from 2 to 4 s, a rating scale appeared for 1500 ms, allowing the participant to judge the level of control she felt over the colour patch. Once the participant made her control judgment, the rating scale was replaced by a fixation cross until the end of the 1500 ms response window. The fixation cross was shown for a 3000 ms inter-trial interval.

Each block ended with a pause lasting 30 s. The experiment consisted of four blocks of 48 trials each. When an error occurred in a trial, the corresponding trial was repeated at the end of each block (up to 10 error trials per block). Repeating error trials ensured that all colours were seen equally often, even if participants made response errors.

Behavioural analyses

Control ratings were analysed using 2 × 2 × 3 × 2 repeated-measures ANOVAs with prime-target compatibility (compatible vs. incompatible) and type of choice (cued vs. free) and action-effect interval (AEI) (short vs. medium vs. long) as within-subjects factors, and group (healthy volunteers vs. patients) as a between-subjects factor. Hits on cued-choice trials, and selection bias (% of prime-compatible responses) on free-choice trials were analysed separately using two 2 × 2 repeated-measures ANOVAs with prime-target compatibility (compatible vs. incompatible) as a within-subjects factor, and group (healthy volunteers vs. patients) as a between-subjects factor. For all analyses, a $p < 0.05$ was taken as the criterion for significance.

Data acquisition and preprocessing

Images were collected using a Siemens 3.0 T Magnetom Trio whole-body scanner. We acquired 290 T2*-weighted echo-planar functional volume per participant over each run. Each volume comprised 33 coronal slices acquired continuously (TR=2000ms, TE=30ms; flip angle=78°, thickness: 3 mm, 23% gap; in-plane matrix size: 64 × 64; voxel size: 3 × 3 × 3 mm^3) were acquired per volume. A high-resolution T1-weighted anatomical image (TR = 2500 ms; TE = 4.77ms; resolution: 1 × 1 × 1 mm^3; matrix size: 256 × 256) was collected for each subject. Head motions were minimized using foam padding and headphones with earplugs were used to dampen the scanner noise.

fMRI data were pre-processed and analysed using using SPM5 software (Wellcome Department of Imaging Neuroscience, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/). The first five volumes of each run were removed to allow for T1 equilibrium effects. All functional volumes were realigned using a six-parameters rigid body transformation to correct for head motions. Functional and structural images were coregistered, and normalized into a standard MNI space (Montreal Neurological Institute

template). Functional data were then smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel, and processed using a 128s high-pass filter.

We included realignment parameters in all statistical analyses as covariates to model out potential non-linear motion-related artifacts (second degree polynomial expansion). Then, we checked data for electronic, and rapid-movements artifacts using the ArtRepair toolbox (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). Artifacted volumes were substituted by linear interpolation between contiguous volumes, deweighted and explicitly modelled in the following statistical analyses. Estimated head movements were small compared to voxel size (<1 mm), and less than 5% of the volumes were excluded due to rapid head movements (>1.5mm/s).

fMRI data analyses

Whole-brain statistical parametric analyses were performed using a two-stage random-effect approach. We estimated independently the model parameters from each subject's dataset and each group of participant, and then made population inferences using the parameter inter-subject variance. Regressors of interest were constructed by convolving functions representing the events with the canonical hemodynamic response function.

For compatible and incompatible conditions of cued and free trials, we defined the 'action selection' phase as the interval between prime onset and participant's response to the mask/target stimulus, and the 'control judgment' phase as the period from the scale onset to participant's rating of their level of control (see **Fig. 1**). Thus, four distinct event-related regressors modelled correct (cued and free) trials associated with compatible and incompatible conditions at both time of action selection and control judgment.

Each participant's control ratings in each compatibility condition were divided into tertiles to define low, medium, and high levels of experienced control (see **Supplementary**

Methods for details). We entered the tertiles into the model (1 = low, 2 = medium, 3 = high level of experienced control) to identify brain regions in which the BOLD signal recorded at (1) time of action selection, and (2) time of control judgment, was modulated by judgments of control. We examined regression coefficients separately for compatible and incompatible conditions of cued and free trials. Additional event-related regressors were used to model and thus remove effects of participants' motor response and RTs in both compatible and incompatible conditions (see **Supplementary Methods** and **Fig. S1**). Finally, scanning series and head motion parameters estimates (translation in x,y,z; roll, pitch, yaw) were included as covariates of no interest in the design matrix.

Regression parameters were estimated in every voxel for each subject, and then parameter estimates were entered in a between-subject, random-effect analysis to obtain statistical parametric maps. Factorial ANOVAs with group (healthy volunteers vs. patients) as a between-subjects factor, and compatibility (compatible vs. incompatible) as a within-subjects factor, compared both groups in cued and free trials separately, either at time of action selection or at time of control judgment. We identified brain activations showing significant contrasts of parameter estimates with a voxel-wise ($P < 0.001$, uncorrected) and cluster-wise ($P < 0.05$, uncorrected) significance threshold (minimum cluster size 10 voxels).

Results

Behavioral performance: Prime-visibility test

Following the main experiment, each group of participants additionally performed a direct assessment of prime visibility inside the scanner (see **Supplementary Methods**, "Prime-visibility test"). One volunteer was excluded from both behavioural and fMRI analyses because her d' in free-choice trials of the prime visibility test was relatively high (0.57, more

than one standard deviation above the mean). For all remaining participants, signal detection analyses confirmed that primes were below the threshold of awareness, with mean *d'* not significantly different from zero in both cued-choice (*volunteers*: mean *d'*= 0.045 ± 0.17, *p* = 0.33; *patients*: mean *d'*= 0.056 ± 0.16, *p* = 0.22) and free-choice trials (*volunteers*: mean *d'*= -0.076 ± 0.21, *p* = 0.18; *patients*: mean *d'*= -0.062 ± 0.2, *p* = 0.26).

Behavioural data: action priming effects on motor response times, and control ratings

Both groups responded faster to compatible than incompatible primes (main effect of compatibility: F(1,26)=10.51, p=0.003), and faster on cued trials than on free trials (main effect of choice: F(1,26)=6.96, p=0.014) (**Fig. S2**). On free trials, participants selected prime-compatible responses significantly more often than prime-incompatible responses (main effect of compatibility: F(1,26)=18.87, p=0.008). There were no group main effects or interactions with group (all p's>0.59) (Fig. S3). Error rates in cued choice trials were unaffected by compatibility (F(1,26)=2.04, p=0.16) and we found no interaction effect between compatibility and group (F(1,26)=0.01, p=0.92) (Fig. S4).

As expected, there was a main effect of compatibility on control ratings: participants experienced higher levels of control over action effects following compatible prime-target associations (F(1,26)=7.78, p=0.01, , η_p^2 = 0.23), consistent with previous findings (e.g., Wenke et al., 2010; Chambon & Haggard, 2012; Chambon et al., 2013). More importantly, we found a significant interaction effect between compatibility and group (F(1,26)=9.32, p=0.005, , η_p^2 = 0.26). This arose because volunteers experienced greater control on compatible relative to incompatible trials, whereas patients with schizophrenia did not (see Fig. 2). There was a significant main effect of the action-effect interval (AEI) (F(2,52) =

181.17, p < 0.001, , η_p^2 = 0.87), with participants experiencing higher control for short AEI (posthoc tests: short vs. medium, medium vs. long, all p's < 0.001). Importantly, we found a significant AEI-by-Group interaction effect (F(2,52) = 15.73, p < 0.001, , η_p^2 = 0.37), with individuals with schizophrenia feeling higher sense of control for short AEI (posthoc test: p < 0.001) but lower sense of control for long AEI (posthoc test: p = 0.001) relative to comparison participants (**Supplementary Information**, **Figure S5**). There was no other significant interaction effects between AEI and Choice and/or Compatibility factors (all F's(2,52) < 0.49, all p's > 0.61). Finally, we found no significant main effect of Choice (cued vs. free: F(1,26) = 0.77, p = 0.38) and no interaction effect between Choice and any other factors (all F's(1-2,26-52) < 1.16, all p's > 0.29).

Importantly, the main effect of compatibility gave a smaller effect size than the main effect of action-effect interval (η_p^2 = 0.23 vs. 0.87, respectively). However, the interaction with group gave similar effect sizes (Compatibility-by-Group: η_p^2 = 0.26 AEI-by-Group: η_p^2 = 0.37).

<< Insert Fig. 2 about here >>

We next computed regressions to investigate whether control ratings could simply reflect monitoring of reaction times. For each participant, we predicted control ratings on each trial from reaction time (β_{RT}), prime compatibility β_{prime} and their interaction ($\beta_{RT*prime}$). We then tested beta values across individuals against zero. In healthy volunteers, prime type significantly predicted the control rating (one-sample t-test: t(1, 13) = -4.22, p = 0.001), but there was no significant relationship with reaction times (t(1, 13) = -1.64, p = 0.12), and no influence of the interaction term β (t(1, 13) = 1.68, p = 0.11). In patients, control ratings were

unrelated to primes (one-sample t-test: $t(1, 13) = 0.18$, $p = 0.68$), reaction times ($t(1, 13) = 0.96$, $p = 0.35$), and their interaction β ($t(1, 13) = 1.15$, $p = 0.27$).

Main effect of action selection

Regions involved in action selection were identified by contrasting compatible and incompatible trials, across both cued and free trials (main effect of compatibility). In order to identify pure effects of action selection, independent of sense of control, we excluded regions which varied with sense of control at time of action selection. To do so, we exclusively masked activations showing a main effect of compatibility (see below) with a parametric contrast of {compatible × control} versus {incompatible × control}, or {incompatible × control} versus {compatible × control}, as appropriate. This contrast identifies regions involved in processing objective fluency (compatible condition) or dysfluency (incompatible condition) of action selection, but whose activity was independent of subjective control experienced by participants (see Chambon *et al*., 2013, for a similar procedure).

In the **cued-choice condition**, a main effect of compatibility was found in bilateral dorso-lateral prefrontal cortex (dlPFC). Specifically, incompatible trials triggered significant deactivation in left (*x, y, z* = –42, 28, 27, Z = 5.74) and right dlPFC (*x, y, z* = 46, 36, 26, Z = 5.07) relative to baseline and compatible trials (**Fig. 3)**. A main effect of compatibility was also found in the right inferior occipital cortex (*x, y, z* = 33, –87, –3, Z = 4.96). The reverse contrast (stronger activation in incompatible than compatible trials) revealed activations in the insular cortex, bilaterally (left: *x, y, z* = 42, 21, –3, Z = 4.46; right: –33, 18, 3, Z = 4.34) and in the fusiform gyrus. The insula activation survived FDR correction for multiple comparisons ($P < 0.05$), while the fusiform activation did not. These results are consistent with studies showing that *subliminally induced* response conflicts do not recruit areas traditionally associated with explicit conflict, such as the anterior cingulate (Dehaene *et al*.,

2003; Chambon *et al*., 2013; but see also Teuchies *et al*., 2016). Finally, the main effect of group did not reveal any significant clusters. The interaction between group and compatibility revealed a single significant cluster in the left precentral gyrus (x, y, z = –21, –21, 63, Z = 3.81), which did not survive correction for multiple comparisons (**Supplementary Information, Supplementary Table S1)**.

In the **free-choice condition**, similar analyses showed a main effect of compatibility in bilateral rostral prefrontal cortex (PFC). Specifically, compatible trials elicited stronger activations in superior parts of left (x, y, z = –15, 49, 43, Z = 4.97) and right rostral PFC (x, y, z = 18, 50, 42, Z = 4.57) relative to incompatible trials (**Fig. 3)**. Incompatible trials, relative to compatible trials, elicited a stronger activation in the inferior orbito-frontal cortex (x, y, z = 27, 36, –9, Z = 3.48) while both the main effect of group and the interaction between group and compatibility elicited activations in the medial part of the PFC (e.g., x, y, z = 12, 51, 33, Z = 3.55), although none of these activations survived FDR correction (**Supplementary Information, Supplementary Table S1)**.

<< Insert Fig. 3 about here >>

Interaction between action selection and sense of control

In both cued and free trials, we identified regions whose activation at the time of action selection, was differentially modulated by levels of experienced control (low, medium, high tertiles of each participant's subjective rating) according to the condition of action selection (compatible, incompatible). These were identified using a parametric contrast of {compatible × control} versus {incompatible × control}, or {incompatible × control} versus {compatible × control}, respectively.

In the **cued-choice condition**, a main effect of compatibility was found in the left angular gyrus (AG). Specifically, left AG (–44, –62, 46, Z = 3.16) was modulated by subjective level of control (low > medium > high) in incompatible but not compatible trials. AG activation did not vary significantly with control on compatible trials. We did not find any regions whose activity increased with *greater* control (high > medium > low) in incompatible trials, even with a very liberal threshold of $p < 0.05$ uncorrected, extent threshold 10 voxels.

Critically, this modulation of AG activity was significantly stronger in healthy volunteers than in patients, as revealed by a significant group × compatibility interaction effect in left AG (x, y, z = –42, –60, 43, Z = 3.81) and, to a lesser extent, right AG (x, y, z = 48, –53, 45, Z = 3.51) clusters. Thus, on incompatible trials, AG activity decreased with increased control in healthy volunteers, while no such modulation of activity was observed in patients (**Fig. 4, and Supplementary Table S2**).

<< Insert Fig. 4 about here >>

In the **free-choice condition**, the group × compatibility interaction was significant in the right AG only (x, y, z = 44, –51, 37, Z = 3.93). Again, incompatible trials triggered a significant decrease in AG activity as a function of increased control in healthy volunteers but not in patients with schizophrenia (**Fig. 5**). Voxels in the right dlPFC (x, y, z = 46, 20, 23, Z = 2.88) also responded to the group × compatibility interaction, but the cluster was far from significance ($P > 0.05$) (**Supplementary Information, Supplementary Table S2)**. In free-choice trials, the main effect of compatibility did not reveal any significant clusters. Finally, the left precentral gyrus was found to be more strongly activated in patients than in healthy volunteers, though this result again did not survive the cluster-level threshold of $P < 0.05$.

<< Insert Fig. 5 about here >>

Functional connectivity (PPI)

We also performed connectivity analyses (PPI) to investigate how mismatch-related coding of agency by AG, and the resulting subjective sense of control, might depend on action selection fluency. Seed voxels were placed in AG regions showing responses related to subjective control, in cued and free choice respectively (see above). PPI analyses were performed separately in both groups (see **Supplementary methods,** "Functional connectivity analyses procedure", for details). We then compared healthy volunteers and patients with schizophrenia directly by contrasting slope coefficients computed from the PPI in each group using a 2 × 2 ANOVA with compatibility (compatible vs. incompatible) as a within-subjects factor, and group (healthy volunteers vs. patients) as a between-subjects factor.

In **cued-choice trials**, the altered action selection caused by prime-target incompatibility triggered a change in the pattern of fronto-parietal interactions in healthy volunteers, but not in patients with schizophrenia. Specifically, in healthy volunteers, incompatible trials induced a significant increase in functional connectivity between left AG and left dlPFC, and between right AG and right dlPFC. Greater activation in left and right DLPFC was associated with lower activation in left and right AG, respectively (left dlPFC, local maximum at –48, 30, 30, $T = 3.89$, $p < 0.005$; right dlPFC, local maximum at 36, 42, 33, $T = 4.25$, $p < 0.001$). No such coupling between AG and dlPFC regions was observed in patients. Finally, comparing slope coefficients between groups confirmed that context-dependent changes (i.e., changes depending on compatibility of action selection) in coupling between AG and dlPFC were significantly stronger in healthy volunteers than in patients with

schizophrenia (left AG-dlPFC coupling: $F(1,13) = 13.3$, $p = 0.003$; right AG-dlPFC coupling: $F(1,13) = 10.41$, $p = 0.006$) (**Fig. 6**).

<< Insert Fig. 6 about here >>

In **free-choice trials**, we found a similar pattern of results, but now involving the medial rather than lateral prefrontal cortex (see below). In healthy volunteers, incompatible trials again triggered a significant increase in functional connectivity between right AG and the superior part of the medial prefrontal cortex (mPFC), with greater activation in mPFC being associated with lower activation in right AG (mPFC, local maximum at –3, 46, 51, $T = 4.01$, $p < 0.001$). Note the mPFC activation found in the PPI is located just between the two rostral PFC clusters found in objective action selection contrasts (see above, **Fig. 3, right panel**). Again, no such coupling between AG and mPFC regions was observed in patients. Finally, comparing slope coefficients between groups confirmed that context-dependent changes in coupling between AG and mPFC were significantly stronger in healthy volunteers than in patients (right AG-mPFC coupling: $F(1,13) = 6.96$, $p = 0.02$).

To recap, our behavioural results suggest a novel dissociation between two levels of action representation in schizophrenia: *objective* motor performance is spared, while the patients show specific deficits for the *subjective*, metacognitive experience of agency. Importantly, the fMRI findings showed that activity and connectivity in a well-established cortical agency network closely mirrored this behavioural dissociation. Thus, we found a main effect of compatibility for both cued (dlPFC) and free (rPFC) choice conditions during action selection, but no group effect, suggesting spared action selection processing in the patients group. However, we also found reduced modulation of the AG activity by agency

ratings in patients compared to healthy volunteers, suggesting *impaired* metacognitive abilities in individuals with schizophrenia. Further, connectivity analyses revealed abnormal information transfer between selection (PFC) and metacognitive (AG) areas in patients with schizophrenia, suggesting that failure of AG to code prospective agency may be due to reduced connectivity with frontal action generation areas.

Discussion

We used subliminal arrow primes to influence the fluency/dysfluency of action selection. As expected, priming influenced both reaction times, and free choices. To investigate the sense of agency, we obtained subjective ratings of control over visual stimuli that followed each action. Importantly, neither primes nor responses alone could predict the colours shown as action outcomes. Instead, compatible primes facilitated, and/or incompatible primes impaired, action selection processing (cf. Wenke *et al*., 2010; Chambon *et al*., 2013; Chambon et al., 2014a, 2014b). Since the primes themselves were not consciously perceived, yet clearly influenced both action selection processing and sense of agency over outcomes, we suggest our result reflect a prospective aspect of sense of agency. Thus, sense of agency may depend on *pre*motor processing before the action, in addition to previously-investigated comparisons between predicted and actual outcomes. Importantly, individuals with schizophrenia showed the same effects of subliminal priming on motor performance, but showed reduced, and even reversed effects of these primes on sense of agency. This finding argues that the subjective feeling of control over action outcomes can be dissociated from motor performance.

Neuroimaging results showed that, for healthy volunteers, the prospective sense of agency was associated with activation of the angular gyrus (AG). Interestingly, stronger AG activations were associated with *lower* ratings of control, suggesting coding for non-agency, rather than for positive agency. The direction of this effect recalls previous experiments involving action attribution judgements, in which AG activation was linked to non-self or/and non-agency, rather than self-recognition or positive agency (Farrer *et al.,* 2002; Farrer *et al.*, 2008). Moreover, there was a distinctive pattern of connectivity between the angular gyrus and frontal action selection areas, which further depended both on prime compatibility. Individuals with schizophrenia showed normal activation of frontal action selection areas.

However, crucially, the patients did not show the connectivity of these areas with the angular gyrus, nor the relation between angular gyrus BOLD response and prospective agency.

Parietal monitoring of multiple frontal signals relating to action selection

To our knowledge, this is the first neuroimaging study to combine prospective sense of agency for two distinct action selection processes, namely cued and free choices. Classically, a lateral frontal route selects responses to external stimuli, while a medial frontal route selects and generates *voluntary* actions (e.g., Passingham *et al*., 2010). We used event-related fMRI to identify brain areas in which selection of cued and free responses was influenced by subliminal priming. The results were broadly consistent with a traditional distinction between externally-triggered and internally-generated routes to action. Incompatible priming for cued choices deactivated the dorsolateral prefrontal cortex in each hemisphere, relative to compatible priming. In contrast, incompatible priming for free choices deactivated a rostral and more medial prefrontal area, again bilaterally. Thus, subliminal priming influenced two classically different routes to action, by modulating activation of whichever frontal regions were engaged in that trial. In each case, activation of the frontal action selection area was reduced under conditions when selection would be dysfluent or difficult. Activation of these areas may therefore reflect the ease of extracting the intended action from a response space (Frith, 2000; Passingham, Rowe, et al., 2004; Barbalat et al., 2009)

Free and cued choice trials were randomised in our design, so switching between these two different circuits for action selection cannot reflect a strategic or preparatory process, but must rather be driven by the cue/mask stimulus occurring on each trial. Interestingly, subliminal primes were presented prior to the target/mask, yet influenced subsequent processing in whichever action selection circuit was engaged by the target/mask, i.e., for either cued or free-choices. This suggests that subliminal priming provided an initial bias

favouring one action representation, but that this representation contributed to circuits for both cued and endogenous action selection. Subliminal primes affected the selection process in a similar way in both cases, and had similar effects on a common metacognitive monitoring circuit responsible for control ratings. These results show that selection processes implemented in multiple frontal circuits for action generation both contribute to prospective agency. Crucially, we found that this prospective contribution of action selection processes was associated with exchange of signals between specific, source-appropriate frontal areas and the AG, at least in healthy volunteers.

The angular gyrus is widely held to underpin the sense of agency (Farrer et al., 2004; Farrer et al., 2008; Nahab et al., 2011; Chambon et al., 2013; Chambon et al., 2015). As in other studies, we found that this coding was clearly negative: stronger activation of AG bilaterally was correlated with a reduced experience of agency. Importantly, this correlation captured a prospective, rather than a retrospective, component of agency, because it was based on a regressor for action selection, rather than action outcome. Variations in the AG BOLD response at the time of action selection predicted subjects' *later* judgements of control in the task, replicating our previous study (Chambon *et al*., 2013). Most previous neuroimaging studies of sense of agency focussed on retrospective attribution of perceptual events to one's own action, or to another agent. These studies reported AG activations when the actual outcomes did not match predicted outcome (e.g., Farrer *et al*., 2008) and disturbances of such signalling in AG in patients suffering from schizophrenia (Farrer et al., 2004). In our study, in contrast, the AG coded for the mismatch between a prime and subsequent target, or subsequent action. The circuitry for monitoring and detecting such *pre*motor mismatches may be comparable to that for detecting mismatch between predicted and actual outcomes. Thus, the involvement of AG in monitoring mismatch between signals may be a general feature common to both prospective and retrospective agency processing.

AG could act as a putative metacognitive hub, monitoring signals generated by a range of different cognitive processes. This general metacognitive monitoring function might explain the wide range of tasks in which AG activation is found (Seghier, 2013).

We used connectivity analyses to investigate how subliminal priming might influence the relation between the prefrontal regions involved in action selection and the AG monitoring circuit. PPI analyses showed that communication between frontal and parietal areas depended strongly on internal premotor signals generated during action selection. Specifically, incompatible priming leads to changes in functional connectivity between prefrontal cortex and AG. In contrast, compatible priming appeared to represent a default situation: we found no additional change in coupling between prefrontal cortex and AG. This does not imply effective disconnection in the compatible condition. Rather, we suggest that prefrontal and parietal areas communicate continuously and by default, but that this communication is transiently increased under conditions of mismatch between competing intentions at the time of action selection, as occurs in incompatible priming.

Dissociation between motor performance and sense of control in schizophrenia

We found a striking dissociation between action selection processing and action selection monitoring in individuals with schizophrenia. Subliminal priming influenced patients' actions, in the same way as for healthy volunteers. Moreover, these behavioural effects were mediated by the same brain activations as in volunteers, namely dorsolateral and rostral prefrontal areas for cued and free-choice respectively. Thus, action selection processing in our patients appeared normal. However the subjective experience of agency that these frontal circuits produced was profoundly altered. We found no effects of subliminal priming on subjective sense of agency in the patient group. That is, the patients appeared not to monitor

prime-induced premotor dysfluency signals, and did not use such signals to prospectively inform their feeling of control over action outcomes. Crucially, this deficit was not due to absence of such premotor signals – since primes had significant effects on the patients' motor response latencies. Instead, the deficit lay in a specific additional process of *monitoring* premotor signals for purposes of constructing action awareness. That is, our data showed a stark dissociation between intact action selection, and deficient metacognitive monitoring of internal action selection processes. Further, our control ratings showed that normal sense of agency over action outcomes partly depends on such metacognitive monitoring (Metcalfe, 2009).

We found a clear correlation between AG activation and prospective sense of control in our healthy volunteers. Consistently, the *absence* of any prospective sense of control in the patients was accompanied by absence of any agency coding in AG. Specifically, the patients' different levels of experienced control were unrelated to AG activation in both compatible and incompatible priming conditions. This was not due to lack of variation in experienced control, since variability across trials in control ratings was comparable in the two groups. We speculate that patients may rely not on prospective action selection to establish a sense of control, but instead rely largely on occurrence of action outcomes. In previous studies, the low-level temporal experience of agency was driven largely prospectively, by predictions about likely outcomes, in healthy volunteers, but largely retrospectively, by actual occurrence of outcomes, in individuals suffering from schizophrenia and its prodromal stages (Voss *et al*., 2010; Hauser *et al*., 2010). The methods in this study cannot conclusively show what signals individuals with schizophrenia used in making agency judgements. However, we observed that patients' control ratings were more strongly driven by variations in action-effect interval, compared to those of healthy volunteers. Patients may compensate for a deficit in prospective signals by relying instead on outcome-related signals, such as temporal

contiguity of outcome and action. Because the action-effect interval is unpredictable, this temporal information can only be available retrospectively, after the outcome has occurred. In summary, individuals with schizophrenia experience varying levels of sense of control, but the sources of this experience are affected by the disease, and show a different balance between prospective and retrospective signals, compared to healthy volunteers. Importantly, action-effect intervals were uniformly distributed across compatible and incompatible trials. Hence, the action-effect interval was orthogonal to the effect of compatibility on control ratings, although the former was significantly stronger than the latter. Interestingly, however, analysis of control ratings showed that the interaction between group and compatibility produced an effect size comparable to the interaction between group and action-effect interval. The schizophrenic deficit in use of prospective cues was approximately balanced by their augmented use of retrospective cues. Thus, our findings converge with those of a previous study using a different task, and different agency measures (Voss et al., 2010; Synofzik et al., 2010).

Altered connectivity underlies deficits in monitoring action selection signals

Modulation of prefrontal-AG connectivity by incompatible priming was entirely absent in patients. Prime-induced intentions did influence the patients' prefrontal action selection process, but did not propagate to the AG monitoring circuit. Specifically, PPI using our action selection regressor did not identify any change in lateral prefrontal connectivity with AG in cued choice, or in rostral prefrontal cortex in free choice. This failure to modulate inter-areal communication may explain the lack of any relation between AG activation and sense of control in the patient group. On this basis, we suggest that the deficit in AG coding in schizophrenia is not primarily anatomical, but rather reflects impaired communication between the disparate set of areas recruited for the current task. In this sense, our data are

consistent with functional disconnection hypotheses of schizophrenia (e.g., Friston, 1998; Barbalat et al., 2011).

In the healthy brain, internal prospective signals may protect us from being surprised by our own actions, and may underlie the feeling of voluntary control (Chambon and Haggard, 2012). We have shown a mechanistic basis in the brain for these internal signals, for both instructed and endogenous action choices, and we have identified the neural circuit that monitors these signals to generate a sense of agency. Most importantly, we have shown that these prospective internal signals are also present in the prefrontal cortex of the brain in individuals suffering from schizophrenia, but that they are not successfully communicated to and monitored by the parietal cortex.

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Table

Table 1. **Clinical and demographic characteristics** (mean ± S.D.)

Characteristic	Individuals with schizophrenia (n=16)	Comparison participants (n=16)	*P* value
Male sex, No. (%)	11 (68,75)	13 (81,25)	0.42
Age, y	32.9 (6.25)	29.9 (6.6)	0.13
SPQ score	30.9 (13.7)	11.5 (10.9)	< 0.001
BACS score	41.4 (5)	41.9 (3.2)	0.68
MWT-B score	29.2 (3.5)	29.9 (5)	0.76
Duration of illness, y	8.07 (4.59)	-	-
SANS score	23.42 (14.08)	-	-
SAPS score	21.6 (19.9)	-	-
Ego-disturbance score[a]	6.1 (4)	-	-
Reality distortion score[b]	9.2 (11)	-	-
Psychomotor poverty score[c]	15 (11.4)	-	-
Disorganisation score[d]	7.8 (8.8)	-	-
Haloperidol equivalent[e]**, mg/d**	3.4 (2.54)	-	-

Abbreviations: SPQ, Scale for Assessment of Schizotypal Personality; BACS, Brief Assessment of Cognition in Schizophrenia; MWT-B, Multiple-choice word test; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

[a] Sum of the following subscores from the SAPS: delusions of mind reading, thought broadcasting, thought insertion, thought withdrawal, somatic delusions, delusions of being controlled, ideas and delusions of reference.

[b] Sum of the scores for hallucinations and delusions from SAPS.

[c] Sum of the scores for poverty of speech, flat affect, and anhedonia/asociality, from the SANS.

[d] Sum of the scores for formal thought disorder and bizarre behavior from the SAPS, and the scores for alogia and inappropriate affect from the SANS (Hardy-Bayle *et al*., 2003).

[e] Depot doses and daily oral atypical antipsychotic drugs at the time of the examination were converted to average daily haloperidol-equivalent doses (Andreasen *et al*., 2010).

Figure legends

Figure 1. Schematic of trial procedure and stimuli. Example trials showing different combinations of the prime-action compatibility in the cued-choice (left and middle) and the free-choice (right) condition. Participants were instructed to respond to the target stimuli and were not informed of the presence of the arrow primes. Primes and masks could appear randomly above or below fixation on each trial. The appearance of the effect was randomly jittered 100, 400, or 700 ms after the keypress to increase the range of judgements of perceived control. After a jittered delay varying from 3 to 5 s, participants were asked to estimate how much control they felt they had over the action effect. Control ratings at the time of judgment were used as modulators of brain activity at the time of action selection. In the three example trials shown, the participant always makes a left hand response. Therefore, in the free choice trial shown, the response is incompatible with the leftward prime.

Figure 2. Action-effect experiment. Mean control ratings on compatible and incompatible trials, for cued and free choice, and for healthy volunteers and patients. All error bars indicate standard deviation. *: $p < .05$. **: $p < .01$.

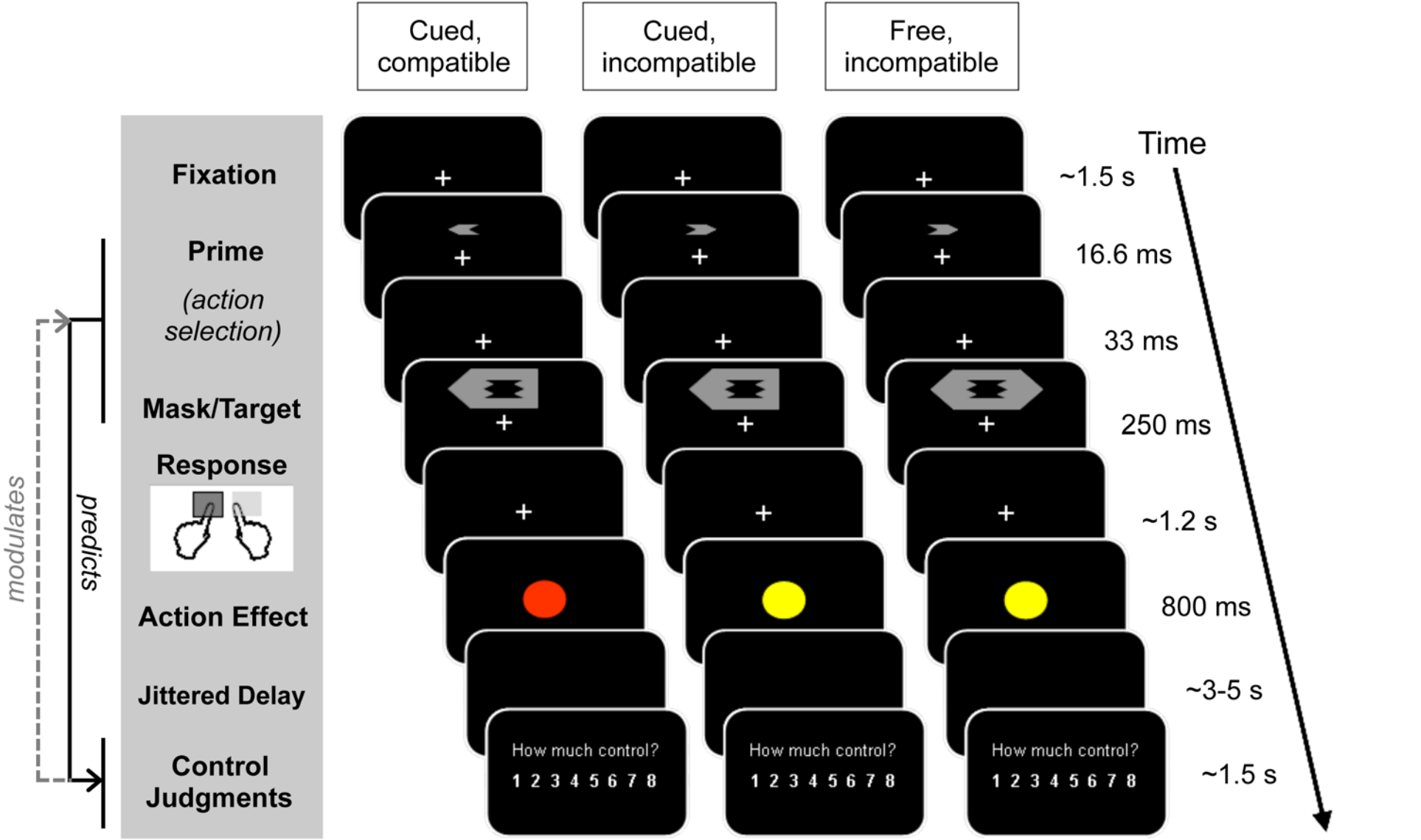
Figure 3. Action-selection regressor: sagittal and axial sections showing brain activations for the main effect of compatibility. Left panel, cued-choice condition: significant clusters were found in dlPFC, bilaterally. Right panel, free-choice condition: significant clusters were found in rostral PFC, bilaterally. Colour bar indicates t-statistic value. Images are presented at a whole-brain threshold of P(false discovery rate) < 0.05, $k >$ 10. A = Anterior.

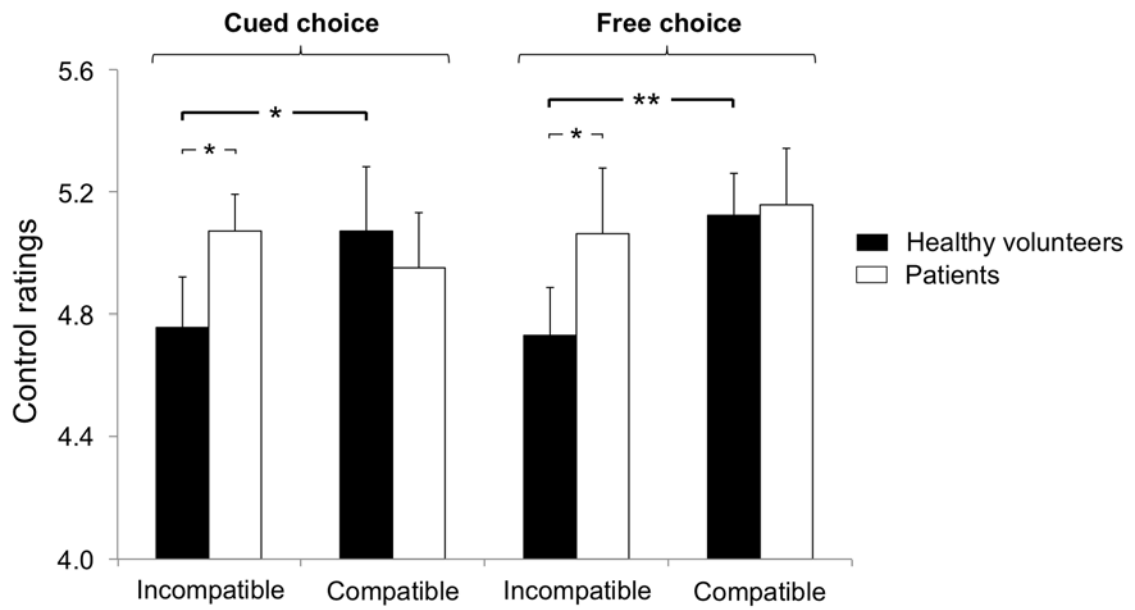
Figure 4. Parametric modulation of angular gyrus activation during action selection by subjective control ratings on cued-choice trials. Results are shown for each combination of group and compatibility. Left and right AG are differentially modulated by control ratings (low, medium, and high) of healthy volunteers, but not patients, participants, depending on how fluent action selection is. A = Anterior. AG = angular gyrus.

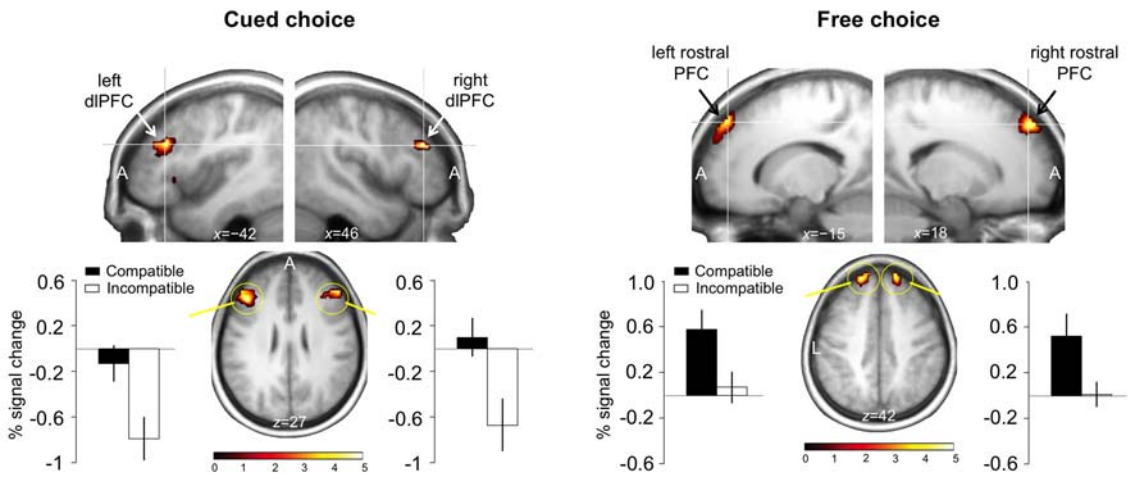
Figure 5. Parametric modulation of angular gyrus activation during action selection by subjective control ratings on free-choice trials. Results are shown for each combination of group and compatibility. The right AG is differentially modulated by control ratings (low, medium, and high) of healthy volunteers, but not patients, depending on how fluent action selection is. A = Anterior; P = Posterior. AG = angular gyrus.

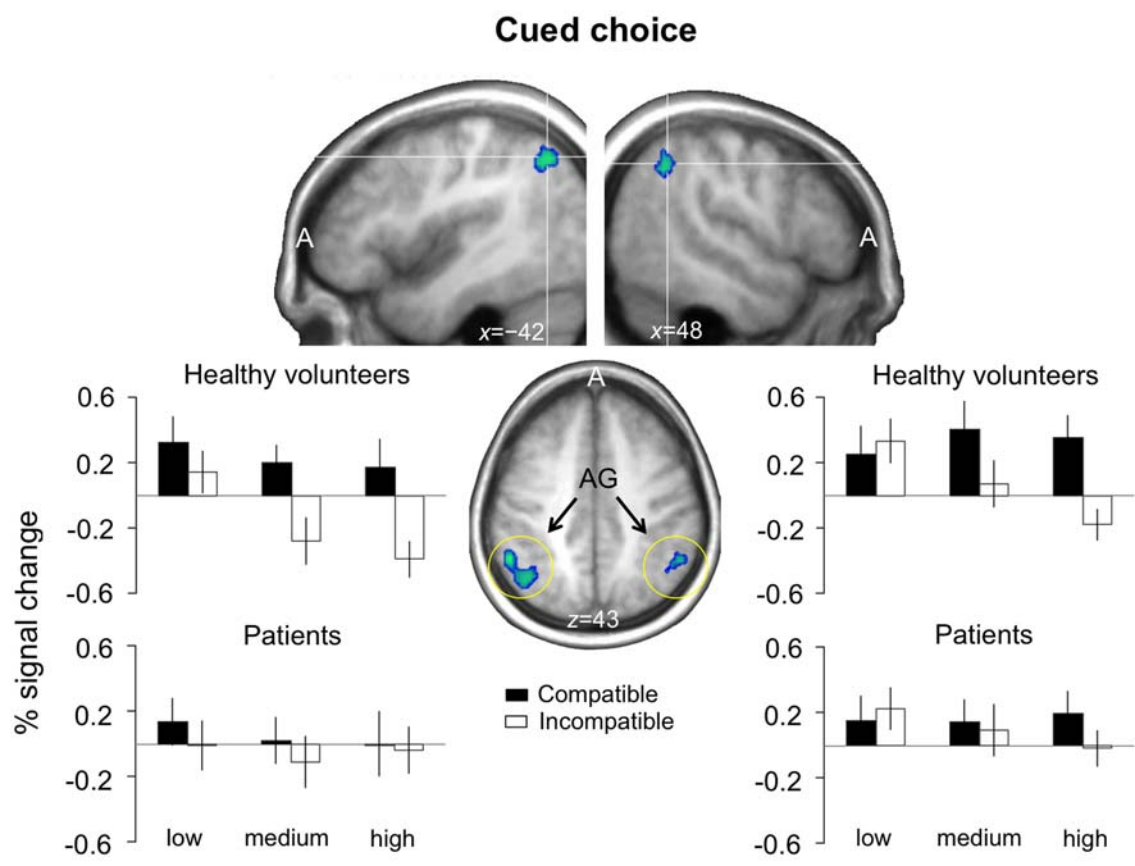
Figure 6. PPI of AG and DLPFC for a single subject in cued-choice trials. Prime-target incompatibility induced a significant increase in functional connectivity between AG and

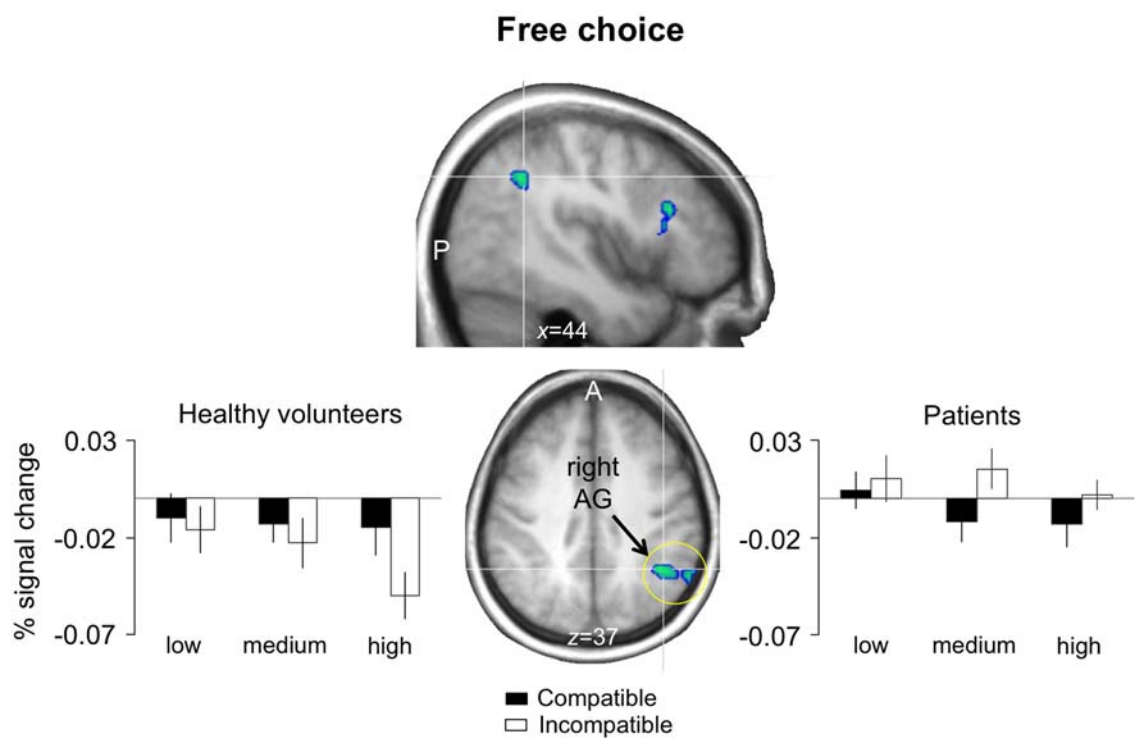
dlPFC bilaterally, in healthy volunteers (middle panels), but not in patients (right panels), participants. Measurements during the INCOMPATIBLE condition: black dots; measurements during the COMPATIBLE condition: grey crosses. Top row: mean-corrected BOLD activity in left DLPFC (peak MNI coordinates, –48, 30, 30) is displayed as a function of mean-corrected BOLD activity in left AG (–42, –60, 43). Bottom row: mean-corrected BOLD activity in right DLPFC (peak MNI coordinates, 36, 42, 33) is displayed as a function of mean-corrected BOLD activity in right AG (48, –53, 45). The difference between regression slopes for the incompatible ($\mathbf{b_i}$) and compatible ($\mathbf{b_c}$) conditions constitutes the PPI. In free-choice trials (not shown here), the same pattern of connectivity between right AG and mPFC was found in healthy volunteers, but not in patients (see PPI results, main text).

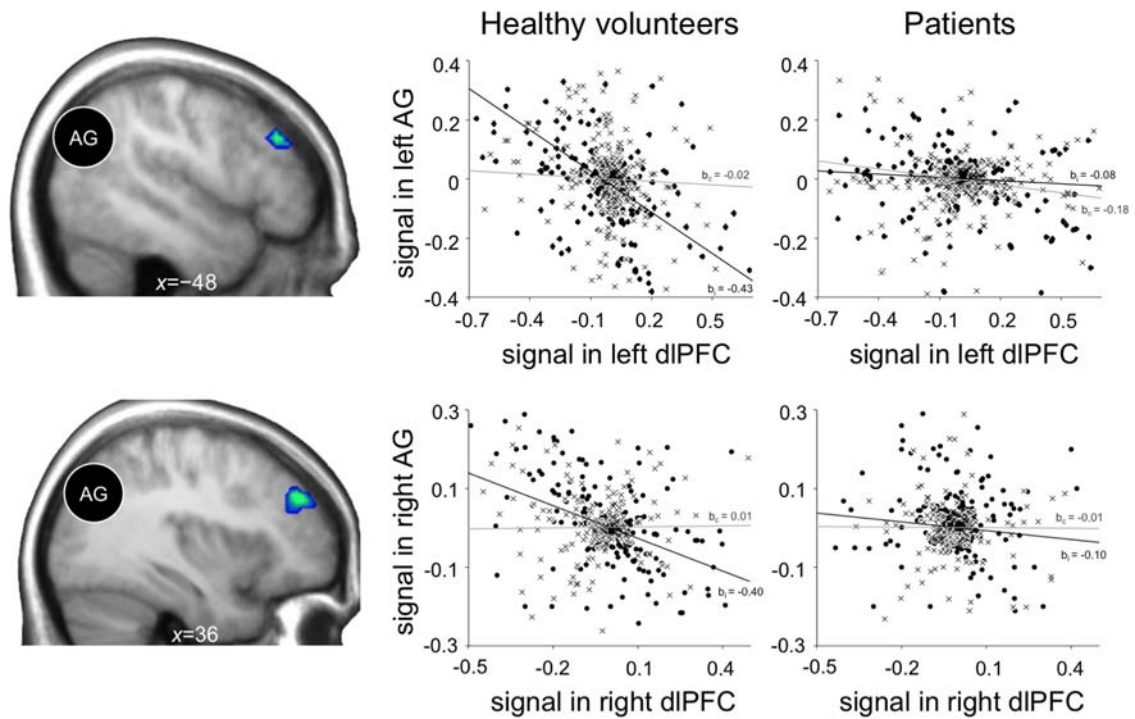

Cued, compatible
Cued, incompatible
Free, incompatible
Time
Fixation
Prime
(action selection)
Mask/Target
Response
Action Effect
Jittered Delay
Control Judgments
modulates
predicts
~1.5 s
16.6 ms
33 ms
250 ms
~1.2 s
800 ms
~3-5 s
~1.5 s
How much control?
1 2 3 4 5 6 7 8


Cued choice
Free choice
5.6
5.2
4.8
4.4
4.0
Control ratings
*
*
**
*
Healthy volunteers
Patients
Incompatible
Compatible
Incompatible
Compatible


Cued choice
left dlPFC
right dlPFC
A
A
x=−42
x=46
Compatible
Incompatible
% signal change
0.6
0.2
-0.2
-0.6
-1
A
z=27
0 1 2 3 4 5
Free choice
left rostral PFC
right rostral PFC
A
A
x=−15
x=18
Compatible
Incompatible
% signal change
1.0
0.6
0.2
-0.2
-0.6
L
z=42
0 1 2 3 4 5


Cued choice
A
x=−42
A
x=48
Healthy volunteers
0.6
0.2
-0.2
-0.6
A
AG
z=43
Healthy volunteers
0.6
0.2
-0.2
-0.6
% signal change
Patients
0.6
0.2
-0.2
-0.6
low
medium
high
Compatible
Incompatible
Patients
0.6
0.2
-0.2
-0.6
low
medium
high


Free choice
P
x=44
A
right
AG
z=37
Healthy volunteers
Patients
% signal change
0.03
-0.02
-0.07
low
medium
high
Compatible
Incompatible


Healthy volunteers
Patients
AG
x=−48
AG
x=36
signal in left AG
signal in left dlPFC
signal in right AG
signal in right dlPFC
b1 = -0.02
b1 = -0.43
b1 = -0.08
b1 = -0.18
b1 = 0.01
b1 = -0.40
b1 = -0.01
b1 = -0.10