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Title: Abnormal intrinsic and extrinsic connectivity within the magnetic mismatch negativity brain network in schizophrenia: a preliminary study.

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Abstract

Altered neuroplasticity is increasingly invoked as a mechanism underpinning dysconnectivity in schizophrenia. We used Dynamic Causal Modelling to compare connectivity during the magnetic auditory Mismatch Negativity (MMN), an index of error prediction, between schizophrenia patients and controls. Patients showed reduced intrinsic connectivity within the primary auditory cortex suggestive of impaired local neuronal adaptation and disrupted forward and backward extrinsic connectivity throughout the MMN network indicative of reduced higher order input in disambiguating activity in lower network nodes. Our study provides the first empirical description of the dysplastic changes underpinning dysconnectivity between primary sensory and higher order cortical areas in schizophrenia.

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1. Introduction

The auditory Mismatch Negativity (MMN) is a neuronal response time-locked to the presentation of a novel (oddball) stimulus embedded within a train of repeated (standard) stimuli. According to the adaptation theory, the standard stimuli produce experience-dependent adaptation in feature-specific neurons against which incoming stimuli are contrasted. The oddball stimulus elicits a neural mismatch response compared to this sensory memory trace (Näätänen et al., 1999). The adjustment model hypothesis introduces the notion of a supramodal "model" of the environment, which integrates the sensory memory of stimuli with wider, experience-dependent contextual information thus including predictions about future events. An oddball stimulus generates a mismatch response because it violates model predictions regarding stimulus trains and requires the model to be adjusted in order to assimilate the new event (Winkler et al., 1996). Recently these theories were synthesised under the framework of predictive coding (Friston, 2005). Predictive coding posits that sensory processing is optimised through hierarchical strategies; backward connections from higher- to lower-order cortical areas relay predictions of lower-level neural activities, whereas forward connections transmit information about the accuracy between predicted and actual lower-level activities. Garrido and colleagues (Garrido et al., 2008; 2009) used Dynamic Causal Modelling (DCM; Friston, 2003) to demonstrate that the auditory MMN is generated: (a) within a hierarchically organised cortical network with key nodes located in primary auditory cortex (A1), superior temporal gyrus (STG) and inferior frontal cortex (IFG); (b) through changes in experience-dependent connections both within (intrinsic) and

between (extrinsic) these regions relating to prediction errors elicited by oddball stimuli (Garrido et al., 2008). As the MMN indexes experience-dependent changes in connectivity within cortical circuits there is renewed interest in this paradigm as a sensitive, non-invasive probe of “neuroplasticity” (Baldeweg et al., 2006). Neuroplasticity can be conceptualized in different ways, but as used here it refers to altered functional coupling within cortical circuits as a function of experience (Stephan et al., 2009a). Altered neuroplasticity is increasingly invoked as a mechanism underpinning dysconnectivity in schizophrenia (Bullmore et al., 1997; Stephan et al., 2009a). It is therefore noteworthy that deficient MMN is a robust finding in schizophrenia which also shows evidence of disease specificity (Javitt et al., 2008).

Based on these considerations we examined whether MMN deficits in schizophrenia index abnormalities in brain connectivity arising from disruption in experience-dependent neuroplasticity either at the level of intrinsic or extrinsic connectivity or both. To test these hypotheses we used Dynamic Causal Modelling to compare connectivity during the magnetic auditory MMN between patients with schizophrenia and demographically matched healthy controls. We obtained data from young patients at the early stages of the disorder to minimise the potential confound of illness duration (Umbricht and Krljes, 2005).

2. Methods and Materials

2.1 Subjects

Fourteen patients fulfilling Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) (APA, 1994) criteria for schizophrenia were recruited from the Highfield Adolescent Unit, Warneford Hospital, Oxford and were matched to twelve healthy volunteers who had no personal history of psychiatric disorder and no history of psychosis in their first-degree relatives (Table 1). Details of recruitment and assessment are shown in Supplementary Material. The study was approved by the Berkshire Research Ethics Committee. All participants and their parents or guardians, as appropriate, provided written informed consent.

2.2 Experimental design

We used an auditory roving 'oddball' paradigm developed and validated by Garrido et al. (2008) and described in detail in Supplementary Material.

2.3 MEG acquisition and analysis

MEG data were recorded with a sampling rate 1000Hz and a 0.03 to 330Hz anti-alias filter was applied. Eye blinking was corrected using principal component analysis and data were filtered between 0.5 to 30 Hz and down-sampled to 200 Hz. Event-related fields (ERFs) were constructed for standard and oddball tones for the peri-stimulus window -100 to 400ms. The MMN was defined as the difference between the standard and the oddball tone. MMN MEG data for each subject were transformed to scalp-map images through linear interpolation and smoothed at FWHM of 6:6:4.

2.4 Dynamic causal modelling

We specified 3 models: (a) Forward model, according to the adaptation hypothesis, (b) Backward model, according to the adjustment hypothesis, and (c) Combination model according to the framework of predictive coding (Figure 1). All models were constructed, fitted and compared for each of the participants as described in detail in Supplementary material.

We used a random effects Variational Bayes approach to select amongst competing models employing the computation of exceedance and posterior probability maps for group level inference. In order to quantify the strength of effective connectivity and its modulations we used random-effects Bayesian Model Averaging (BMA) to compute average connectivity estimates across all models and all subjects (Stephan et al., 2009b).

3. Results

3.1 MMN results

The grand average ERF to standard and oddballs for each group are illustrated in Figure 2A and 2B. Significant group differences were found in the MMN time window 150 to 360 ms over frontal and central areas (Figure 2C; Figure 3).

3.2 Model comparison

As anticipated (Garrido et al., 2008) in healthy controls the Combination model outperformed both the Forward and Backward models with exceedance probability of 89%. The Combination model assumes that the MMN response emerged from changes in all bidirectional extrinsic as well as in intrinsic connections. In patients the optimal model included modulation via the MMN of the intrinsic connections and only the forward connections, which was the Forward model. The exceedance probability for this model was 44%, surpassing the exceedance probabilities of the other two tested models.

3.3 MMN modulatory parameters

The BMA values are shown in Figure 4a and 4b for the controls and patients group respectively. Table 2 summarizes the connection parameter estimates from each group obtained after BMA and the effect size of the case-control differences.

4. Discussion

4.1 Abnormal intrinsic and extrinsic connectivity in temporal lobe sources during MMN generation in schizophrenia

During the roving paradigm each oddball tone is repeated after its first presentation thus becoming a standard tone. In healthy individuals this transition is associated with neuroplastic changes resulting in increased intrinsic connectivity within A1 and in extrinsic connectivity to the STG. Intrinsic changes reflect local neuronal adaptation that relates to concepts of sensory memory and extrinsic changes are considered relevant to sensory learning (Garrido et al., 2009).

The largest effect size for the difference between patients and controls was noted for the intrinsic connections within the A1, particularly on the right. We suggest that this finding reflects loss of local adaptation within the feature-specific neurons in the primary auditory cortex resulting in deficient sensory memory. This notion is supported by Wible et al. (2001) who found abnormally increased activation in the primary auditory cortex in patients with schizophrenia during the presentation of trains of standard tones. Additionally Baldeweg et al. (2004) reported that patients with schizophrenia do not benefit from experimental manipulations known to strengthen sensory memory as they did not evidence MMN enhancement with increasing length of standard tone trains.

Abnormalities in patients' ability to form or sustain a memory trace should reduce change detection to the oddball stimulus and thus the connectivity of the primary

sensory to secondary association areas. Accordingly patients showed reduced modulation of the forward connection from the A1 to the STG. The STG is considered a key node for the early detection of auditory mismatches and the strength of the connectivity between from A1 to STG normally increases when the auditory input does not match predictions (Gariddo et al., 2009). Taken together our results point to deficits in sensory memory formation leading to inefficient processing of auditory information within primary auditory cortices and reduced precision in error.

4.2 Abnormally increased backward frontotemporal connectivity during MMN generation in schizophrenia

In healthy individuals, the backward connection from the IFG to the STG during the MMN shows a negative modulation which has been interpreted as an inhibitory effect relating to suppression of the prediction error (Garrido et al., 2009). In patients this inter-regional coupling was increased and showed reverse (positive) polarity. This resonates with the findings by Winterer et al. (2003) who also observed a negative frontotemporal path coefficient in normal controls and a positive in patients with schizophrenia. This positive modulation in patients is suggestive of a loss of higher-order signals disambiguating activity in lower areas.

The abnormalities in frontotemporal interactions observed during the MMN possibly represent another facet of the frontotemporal dysconnectivity observed in schizophrenia across a number of paradigms and methods (Meyer-Lindenberg et al., 2001; Stephan et al., 2009a).

4.3 Implications for neuroplasticity and dysconnectivity in schizophrenia

Our findings provide the first empirical description of the dysplastic changes underpinning dysconnectivity between primary sensory and higher order cortical areas in schizophrenia. They also highlight the importance of early perceptual processing deficits for schizophrenia (Näätänen and Kähkönen, 2009). This is in line with imaging data suggesting that during perception patients with schizophrenia are less likely to employ hierarchical strategies in which higher cortical areas relay information restraining and disambiguating incoming sensory data based on previous experience (Dima et al., 2009; 2010).

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Figure Legends

Figure 1. Model specification: The sources comprising the models were: A1: primary auditory area; STG: superior temporal gyrus; IFG: inferior frontal gyrus; L: left; R: right. Three models with five areas were specified with bidirectional endogenous connections between all regions (L_A1, R_A1, L_STG, R_STG, R_IFG), intrinsic connections in the A1s and with driving input of 'standard and oddball tones' into the A1 bilaterally. Schematically, the modulation MMN is represented as dashed lines in the bidirectional endogenous connections and as grey colour in the intrinsic connections. The three models are: (i) Combination model that has all connections modulated, (ii) Forward model that has the intrinsic and forward connections modulated and (iii) Backward model that had the intrinsic and backward connections modulated.

Figure 2. A. Grand average ERF waveforms for standard and oddball tones in the patient group (n=14) for a MEG channel corresponding broadly to Cz location. **B.** Grand average ERF waveforms for standard and oddball tones in the controls group (n=12) for the same channel. **C.** MMN waveforms (standard minus oddball tones) for the control and patient group at the same location.

Figure 3. Characterisation of the MMN difference wave: comparison between patients suffering from schizophrenia and healthy controls. **A.** SPM showing increased response to the MMN in controls relative to patients ($p < 0.001$ uncorrected). This analysis searched for spatio-temporal differences over 2D sensor-

space and all peri-stimulus times (–100 to 400 ms). Significant effects were found over temporal and frontal areas in the range 110 to 320 ms peaking at around 200 ms. **B.** Difference topographic maps of the MMN waves (standard minus oddball tones) for controls minus patients.

Figure 4. Mean coupling changes (BMA, averaged across subjects in each group) lie beside the connections in the graph for healthy controls and patients. A1: primary auditory area; STG: superior temporal gyrus; IFG: inferior frontal gyrus; L: left; R: right.

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Conflict of Interest

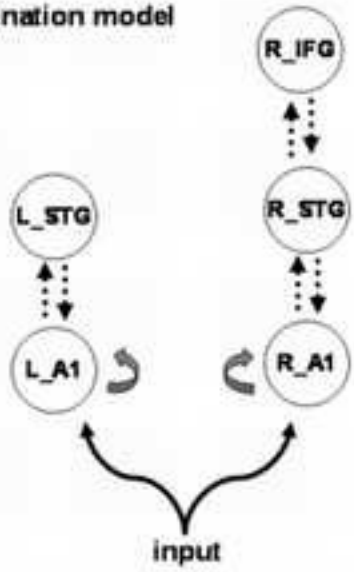
The authors declare that they have no conflicts of interest.

Contributors

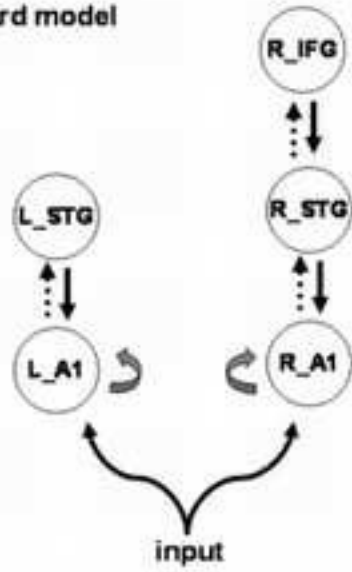
Drs Dima, Braeutigam, Frangou and James were involved in the conceptualisation of the study. Dr. Braeutigam adapted the roving oddball paradigm for MEG. Drs. Dima, Braeutigam, Burge and James performed patient recruitment and data collection. Dr. Dima and Dr. Frangou conducted the data analysis and wrote the first draft of the manuscript, which was edited by Drs. Braeutigam and James. All authors contributed to and have approved the final manuscript.

Figure(s)
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Combination model



Forward model



Backward model

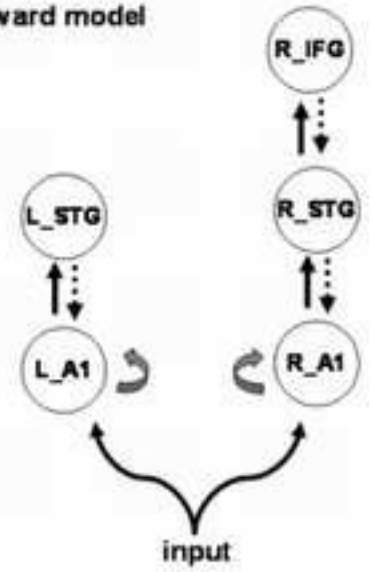


Figure 2
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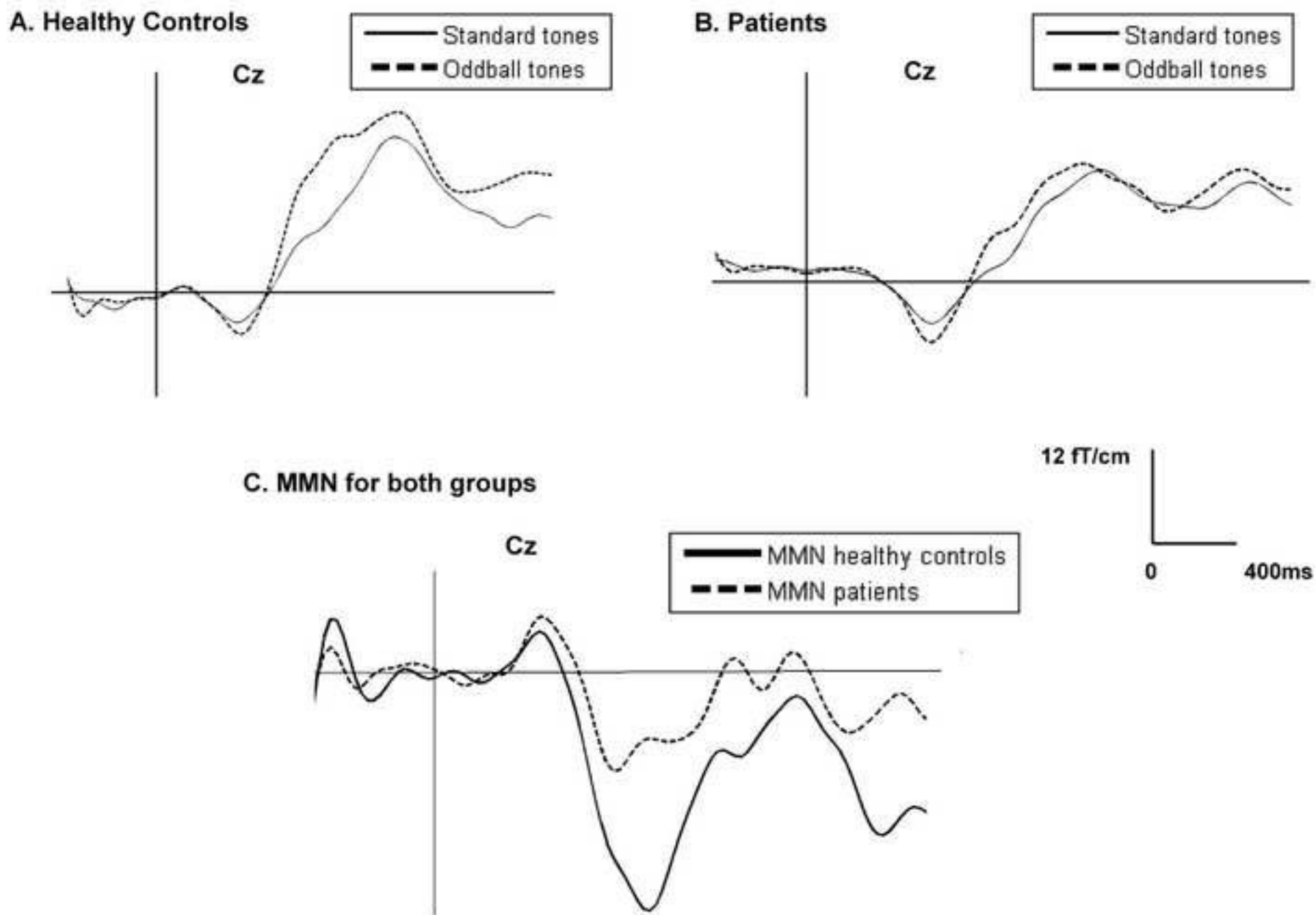
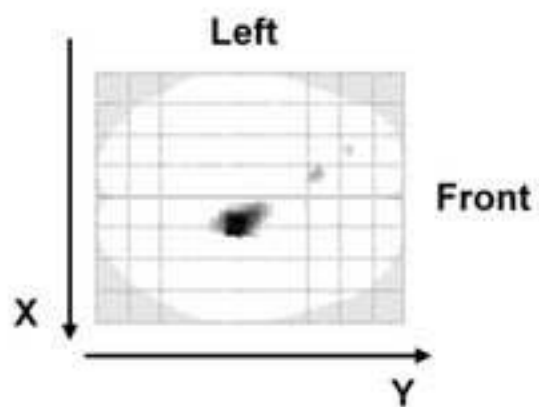
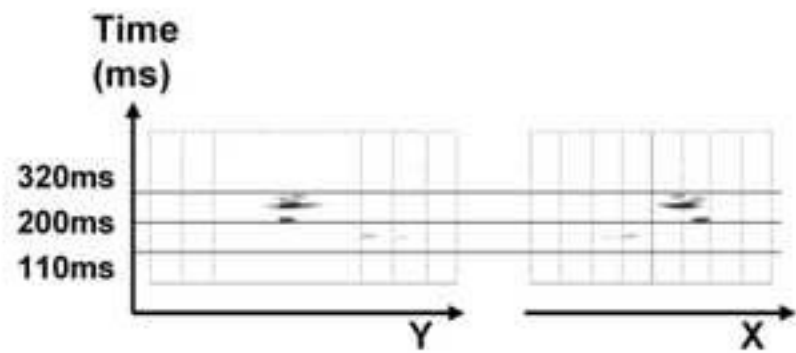


Figure 3
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A.



B.

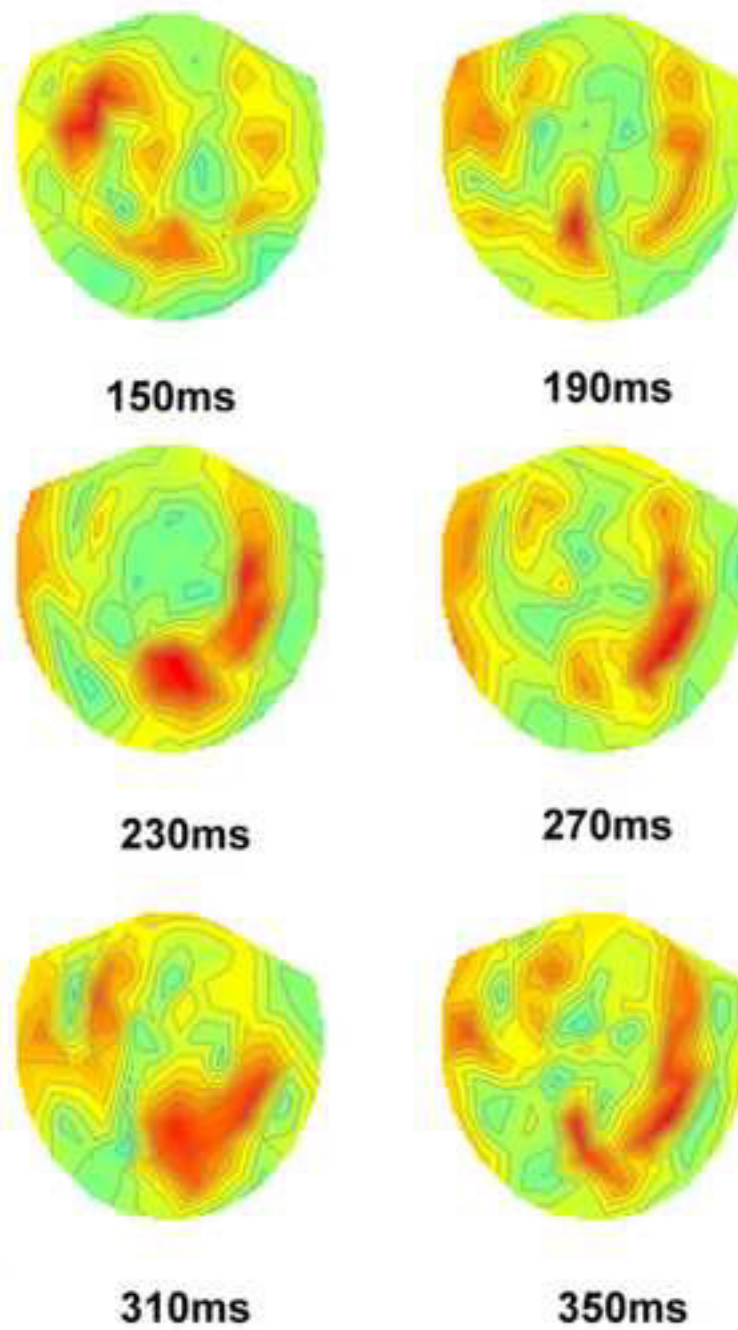
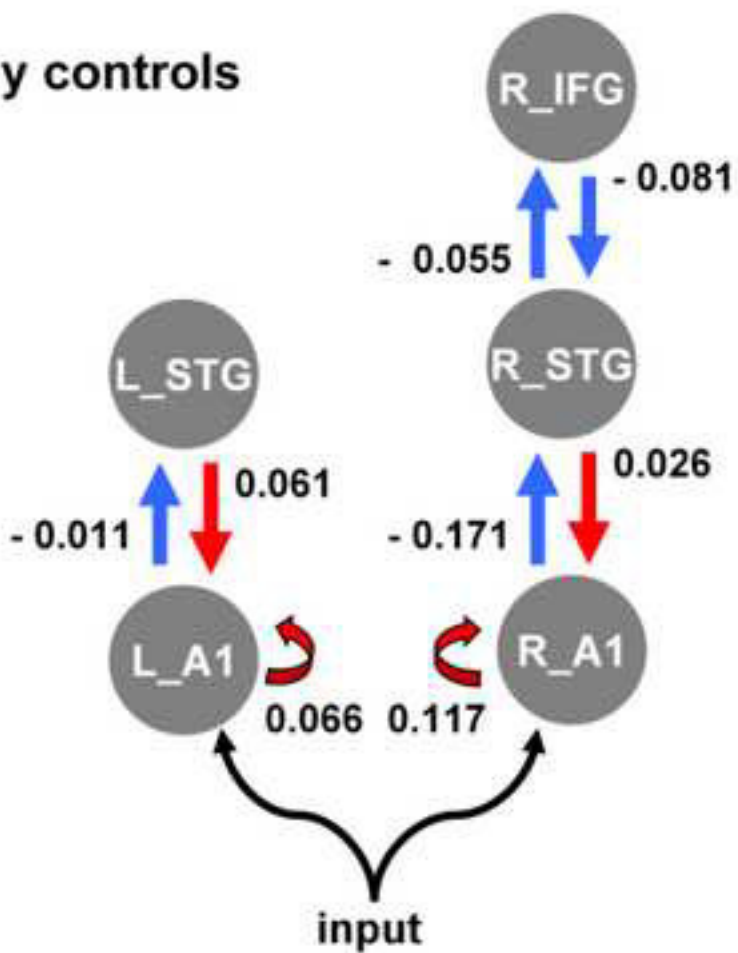
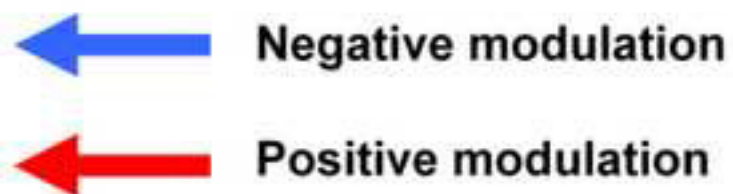
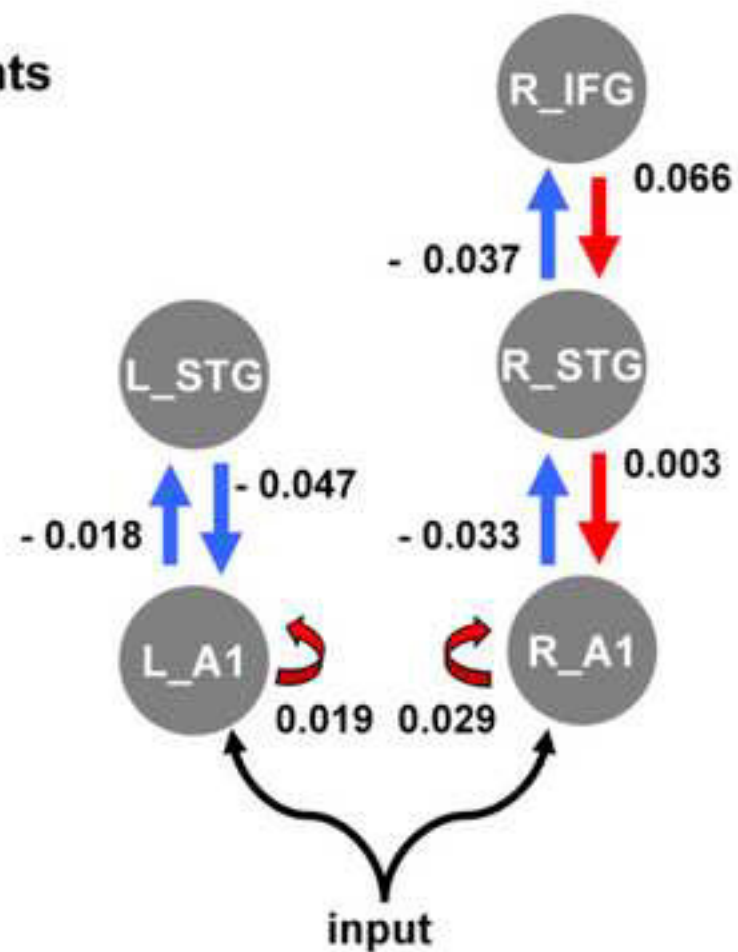


Figure 4
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Healthy controls



Patients



Role of the funding source

This study was supported by the Medical Division of Oxford University. The Medical Division had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit this paper for publication.

Table 1: Demographics and psychopathology data.

	Patients N=14	Controls N=12	Statistics
Male:Female	8:5	5:7	Fisher's exact test, p=0.69
Age	17.1 (0.9)	16.2 (1.9)	t = 1.65; p = 0.112
Handedness R:L	13:1	10:2	Fisher's exact test, p=0.58
WASI IQ	96 (15)	112 (9)	t = 2.44; p = 0.027
Positive PANSS score	22.1 (3.6) ¹	-	-
Negative PANSS score	12.57 (5.5) ²	-	-
General PANSS score	34.7 (5.1) ³	-	-
Age of onset (in years)	16.2 (1.2)	-	-
Duration of illness (years)	1.01 (0.95)	-	-
Medication (mg/day; CPZE)	275 (95)	-	-

For continuous variables data shown are mean (standard deviation);

PANSS= Positive and Negative Syndrome Scale; **WASI**= Wechsler Abbreviated Scale of Intelligence;

CPZE= chlorpromazine equivalents;

¹ Positive PANSS scale range: 16-29; ² Negative PANSS scale range: 7-30; ³ General PANSS scale range:

Table 2. Mean (standard deviations) BMA MMN modulatory estimates for all connections across the three models in the controls and patients group.

Connection type	Healthy Controls (n=12)	Patients with Schizophrenia (n=14)	Absolute effect size of the BMA differences between patients and controls	P-values
<i>MMN Modulatory parameters</i>				
LA1	0.066 (0.115)	0.019 (0.064)	0.54	0.20
RA1	0.117 (0.078)	0.029 (0.108)	0.96	0.02
LA1→LSTG	-0.011 (0.295)	-0.018 (0.198)	0.03	0.94
RA1→RSTG	-0.171 (0.236)	-0.033 (0.280)	0.55	0.18
LSTG→LA1	0.061 (0.257)	-0.047 (0.358)	0.36	0.37
RSTG→RA1	0.026 (0.242)	0.003 (0.321)	0.08	0.83
RSTG→RIFG	-0.055 (0.180)	-0.037 (0.214)	0.09	0.82
RIFG→RSTG	-0.081 (0.118)	0.066 (0.222)	0.84	0.04

BMA=Bayesian Model Average; **MMN**=Mismatch Negativity; Relative size of Cohen's d (Cohen, 1988):

negligible effect (≥ -0.15 and < 0.15), *small* effect (≥ 0.15 and < 0.4), *medium* effect (≥ 0.4 and < 0.75) and *large* effect (≥ 0.75 and < 1.10)