

Research Article Ερευνητική εργασία

Cortical thickness and oscillatory phase resetting: A proposed mechanism of salience network dysfunction in schizophrenia

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Schizophrenia is characterised by both electrophysiological abnormalities and consistent changes in the structure of cortical grey matter. But the relationship between these two observations is largely unknown. Structural changes reported in schizophrenia include reduced grey matter volume, thickness and surface area in several cortical regions, but most frequently in the insula and anterior cingulate cortex. These two regions together constitute an intrinsic brain circuit known as the "Salience Network", which has a key role in stimulus processing. During stimulus processing tasks, evoked activity is noted using electroencephalography (EEG). Phase resetting of ongoing oscillations contributes to this evoked activity. Neuronal oscillations play a crucial role in cerebral recruitment during cognitive tasks, and influencing the oscillatory phase can modulate cortical excitability and the transition between various cognitive states. At a network level, such a transition or switch is thought to be enabled by the Salience Network. In this study, we investigated the relationship between the cortical thickness in the Salience Network (measured using MRI) and the degree of phase resetting observed during an oddball task (measured using EEG) in 18 medicated male patients in a clinically stable phase of schizophrenia and 20 age and gender matched healthy controls. We obtained a measure of partial phase resetting after a stimulus is presented, and a second measure representing mean evoked activity, using the methods proposed by Martinez-Montes. Using MRI analysis, we have firstly shown that there is a significant loss of cortical thickness of regions that constitute the Salience Network in patients with schizophrenia. EEG analysis revealed that in healthy controls, the expected relationship between phase resetting and evoked electrical activity is observed, but in patients with schizophrenia the theta phase resetting is a weak predictor of the activity evoked by attending to a target stimulus, though the difference between the groups did not reach statistical significance in the present sample. Furthermore, in patients with schizophrenia the reduced thickness in the Salience Network is associated with the inefficient phase resetting of theta oscillations. Our findings suggest that the grey matter reduction seen in the Salience Network in patients with schizophrenia has substantial functional consequences. In particular, the structural defect of the insula that is seen in schizophrenia is likely to be associated with less efficient recruitment of brain circuits for processing information. This implies a possible mechanism by which disruptions in the intrinsic Salience Network can result in a general disturbance in salience detection seen in schizophrenia.

Key words: Salience network, phase resetting, oscillations, insula, cingulate.

Introduction

Voxel based morphometry (VBM) in chronic schizophrenia consistently shows significant reduction in the grey matter volume in the insula and the anterior cingulate cortex.^{1,2} Structural changes in these two regions are thought to be important in the pathophysiology of schizophrenia.³ In particular, insula shows significant grey matter reduction in patients with at risk mental state who later develop schizophrenia-like illness,^{4,5} and thus predicts transition from prodrome to established psychosis.⁶ The mechanism by which such a consistent grey matter loss across the insula and ACC influences the clinical and neuropsychological features of schizophrenia remains unknown.

Anterior insula and anterior cingulate constitute a "Salience Network", one of the three major intrinsic connectivity networks (ICN) identified using functional connectivity analysis in healthy individuals.⁷ Along with other ICNs (Central Executive Network (CEN) comprised of dorsolateral prefrontal cortex and the intraparietal sulcus and Default Mode Network (DMN) comprised of medial prefrontal cortex and posterior cingulate cortex), the Salience Network (SN) is involved in attentional modulation and information processing.⁷ The DMN includes a set of regions related to a "resting" mode of introspective mental activity.^{8,9} These regions characteristically show reduced neural activity when attending to tasks. In contrast, during task performance, both the SN and the CEN are activated.¹⁰ The SN is thought to act as a system equipped to identify the most homeostatically relevant material from a myriad of internal and external stimuli occurring in multiple modalities. Thus the SN sets up the executive network to operate or not on identified stimuli. Using latency analysis for Blood Oxygen Level Dependent (BOLD) activation patterns Sridharan et al¹¹ demonstrated temporal precedence of insular activation during event transitions and in resting state. Further, Granger causality analysis from the above study suggests that insular activation causes BOLD activations across the nodes in the executive network and deactivations across the nodes in the default mode network.

Clinical and experimental evidence strongly suggest attentional and information processing defi-

cits in schizophrenia. Attention to both behaviorally relevant targets and infrequent and/or novel but distracting non-targets are affected in schizophrenia.^{12,13} Higher distractibility from non-targets has been noted¹⁴ in addition to higher degree of errors induced by non-relevant cues during target detection.¹⁵ This pattern of attentional deficits is highly suggestive of a failure in both effective reorientation to relevant stimuli (i.e. salience detection) and executive control of evaluating the identified stimuli.^{16,17}

Electrophysiological investigations have contributed significantly to our understanding of stimulus processing and attention system. In particular, oscillatory activity of brain has been shown to have major role in the cognitive processes related to attention, working memory and sensory perception, although the relative contributions of background oscillations and additive electrical activity in event related potentials remains a subject of debate.¹⁸ In addition to amplitude and spectral power, much information is contained in the phase of oscillations.^{19,20} Phase of ongoing oscillations at the time of stimulus presentation potentially influences the identification of a near-threshold stimulus.²¹ Degree of phase locking of various frequency bands at frontal, parietal and somatosensory areas could differentiate the consciously attended stimuli from unperceived stimuli in different sensory modalities.^{22,23} Thus a mechanism that sets or resets the phase of ongoing neuronal oscillations can influence attentional salience by modulating the excitability across cortical regions. In particular, phase resetting of ongoing theta oscillations has been shown to influence attention irrespective of the modality of stimulus presentation.²⁴

In schizophrenia, deficits in phase resetting have been recently demonstrated.²⁵ Using an auditory paired-click paradigm, Brockhaus-Dumke et al²⁵ showed that phase resetting in lower frequency bands is significantly reduced in schizophrenia, and this effect is noted across a broad time-window before and after stimulus presentation. Abnormalities in mean amplitudes of low-frequency oscillations that are time-locked to a stimulus have been well-documented.²⁶ In particular, the theta oscillations that occur 200 ms to 500 ms after a task-relevant stimulus are reduced.²⁷ We recently reported evidence that part of the reduction in the evoked low

frequency oscillations can be explained by deficits in the phase resetting seen in schizophrenia.²⁸

In summary, functional connectivity studies implicate insula and the SN in enabling the switch between task-positive and task-negative networks. On the other hand, electrophysiological studies implicate the mechanism of phase resetting of theta oscillations in this switching process that reorients the focus of attention. In schizophrenia, where abnormalities have been reported both in the SN and in phase resetting, we hypothesised a relationship between anatomical deficits in the SN and the defects in phase resetting of ongoing theta oscillations when attending to a stimulus.

Material and method

Participants

Twenty male healthy controls and 19 male patients with schizophrenia were recruited for this study. Regional Ethics Committee (Nottinghamshire) approved the study and all participants provided informed consent. The diagnosis of schizophrenia was made in accordance with Diagnostic and Statistical Manual of Mental Disorders-IV criteria²⁹ in a clinical consensus meeting on the basis of information provided by referring clinicians, review of existing case files and a research clinical interview performed by a trained research psychiatrist. All patients were in a state of clinical stability (defined as no more than 10 points change in Global Assessment of Functioning scale in the 6 weeks preceding the scan). Subjects with neurological disorders, current substance dependence, learning disabilities (IQ < 70 using Quick Test³⁰), and diagnosis of any other axis I disorder were excluded. Signs and Symptoms of Psychotic Illness interview (SSPI) was administered to quantify clinical symptoms by a trained clinician within the same week as EEG and MRI recordings.³¹ All patients were receiving treatment with atypical antipsychotic medications. The healthy control group comprised twenty men free of current axis I psychiatric disorder, and either personal or family history of psychotic disorder, matched group-wise in age and socio-economic status (measured using National Socio-Economic Classification, NSSEC³²) to the patient group. Controls had similar exclusion criteria to patients. Handedness was ascertained

according to the Annett criteria.³³ EEG was carried out immediately prior to the MRI acquisition on the same day for all subjects.

EEG data acquisition

The EEG experiment included presentation of series of 1000 Hz tones (85%) randomly intermingled with higher pitched 1500 Hz target ones (15%) at 80 dB level. Subjects made a button press response to the high-pitched target tones. Each stimulus was of 50 ms duration and 295 stimuli were presented with a fixed inter stimulus interval of 2 s. Subjects undertook a practice session with 30 stimuli prior to the experiment. Scalp potentials were recorded from 128 electrodes (Biosemi, Amsterdam, The Netherlands) spread over the scalp according to the International Five Percent Electrode System for high resolution EEG³⁴ with a sampling rate of 256 Hz. Eye movements and blinks were recorded from electrodes lateral to each eye and an electrode placed below the right eye and another above it.

EEG data preprocessing

Processing of EEG data was carried out using Vision Analyzer 1.05 (Brain-Products, Munich, Germany). All electrodes were re-referenced to the averaged electrical potential of two electrodes on the mastoids. In order to eliminate slow drifts and high frequency noise, EEG data were band-pass filtered 0.5–50 Hz using phase-shift-free Butterworth filters with a 48 dB/octave slope. The data were corrected for eye blink artefacts according to Gratton et al³⁵ and stimulus-locked segments were extracted for correctly hit target trials. Large segments (1000 ms before and after stimulus) were created in order to allow for the time-frequency analysis. Artefact rejection was performed to eliminate trials contaminated by non-blink artefacts such as excessive muscular activity. Specifically, trials with a voltage greater than 100 μ V were rejected automatically. The number of trials remaining after the artefact rejection did not differ between the two groups: targets-controls=45.24 (S.D. 8.52), targets-patients=44.98 (S.D. 7.22).

EEG data analysis

Analysis of EEG data to obtain measures of phase resetting and mean evoked (time-locked) activity in the theta band was carried out using the methods

proposed by Martinez-Montes et al³⁶ We initially extracted a representation of the time varying signal in the mid-theta range using a complex Morlet wavelet transformation of the segmented data around the centre frequency 6 Hz and with a Gaussian frequency spread of 2 Hz half-width, for the target trials. The choice of the centre frequency was based on our previous analysis.²⁸ We obtained T-phase, representing partial phase resetting after a stimulus is presented, and T-mean, representing mean evoked activity. In contrast to the commonly measured Inter-Trial Coherence, T-phase is a measure of phase resetting that is not confounded by a post-stimulus increase in mean amplitude (see Martinez-Montes³⁶ and Doege et al²⁸). T-phase and T-mean are measures that quantify the relative change in phase and mean amplitude from a pre- to a post stimulus period. For both meas-

ures, the pre-stimulus period was defined as 200 ms to 600 ms before the target presentation, and post-stimulus period was defined as 0 ms to 600 ms after the stimulus presentation. The final T values are the the mean (across the post stimulus period) of the ratio measures for each post-stimulus sample derived according to the original work reported by Martinez-Montes.³⁶ The principle behind these measurements is illustrated in figure 1.

MRI data acquisition

Magnetic resonance scans were collected using a Philips 3-T imaging system equipped with 8-channel phased array head coil. The scanning protocol included a single high-resolution three-dimensional T1-weighted MPRAGE volume of isotropic voxel size $1 \times 1 \times 1$ mm³, flip angle 8°, field of view $256 \times 256 \times 160$ mm³.

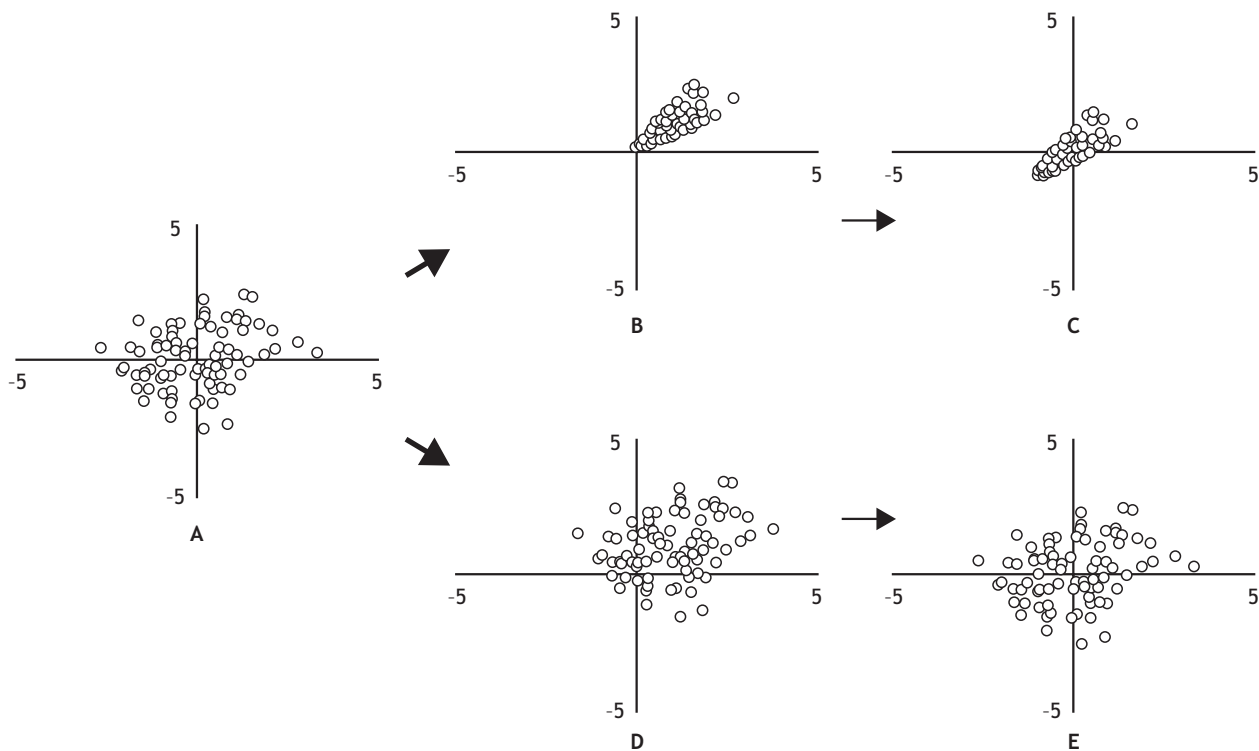


Figure 1. Plots of simulated real and imaginary components of the transformed complex wavelet coefficients. Each dot represents wavelet amplitude and phase at a specific time point, in the complex plane. Plot A represents pre-stimulus period where phases are random with zero mean. Plot B represents a partial phase resetting effect whereby the stimulus results in an alignment of previously random phases into a specified range ($45^\circ \pm 15^\circ$). But when such phase resetting takes place, the amplitude of the mean signal also increases. Plot C shows phase resetting effect after subtraction of the mean signal. Plot D and E represent hypothetical post-stimulus increase in mean without a direct phase resetting effect. Plot D shows that the simple addition of a constant signal to every trial produces a phase clustering effect. Plot E shows that after subtraction of the added signal, the phases are once again randomly distributed.

MRI Image analysis

The T1 weighted images were passed through a series of image processing steps in accordance with the surface based algorithm of Freesurfer image analysis suite.³⁷ Automated parcellations based on Destrieux Atlas that makes use of individual sulcogyral patterns³⁸ were obtained. The anatomical definition of anterior cingulate follows the description given by Vogt et al³⁹ The anatomical definitions of the insular subregions are as follows: The circular sulcus that encircles and forms the outer boundary of the insula is divided into 3 segments: superior segment horizontally limits the insula from the subcentral and inferior frontal gyri, anterior segment vertically limits the insula from the orbital gyri, and inferior segment obliquely limits the insula from the superior aspect of the superior temporal gyrus. The central sulcus of the insula runs antero-inferiorly from the superior segment of the circular sulcus of insula. It divides the insula in two parts: the anterior short insular gyrus and the posterior long insular gyrus. The grey matter of the central sulcus itself is included with the long insular gyrus. Average thickness values across the vertices within the three anteriorly located subregions (anterior insula, anterior and superior segments of the circular sulcus), and the single anterior cingulate segment were obtained from each of the two hemispheres.

Statistical analysis

We hypothesized that: (i) Patients with schizophrenia will have reduced cortical thickness in the Salience Network (ii) Phase resetting of frontal theta oscillations will predict the evoked signal generated during target detection across the two groups. This relationship will be stronger in controls than in patients. (iii) In patients, the reduced grey matter thickness of the Salience Network will be related to frontal theta phase resetting.

To test these hypotheses, we firstly extracted cortical thickness measures across 4 parcellations for each hemisphere-3 subregions of insula and the anterior cingulate as described above. The SN thickness was analyzed using repeated measures analysis of covariance (ANCOVA) with age and global thickness as covariates, diagnosis (schizophrenia and healthy controls) as between-subject factor, and hemisphere

(left and right) and regions (4 SN regions) as within-subject variables. Regional comparisons were carried out using independent t-tests for mean thickness (adjusted for age and global thickness) for each of the 4 parcellations in right and left hemisphere. To test the second hypothesis, a simple linear regression model with T-mean as dependent variable and T-phase as independent variable was constructed in patients and controls separately. A general linear model describing cortical thickness was constructed in the patient sample with hemispheric laterality (right and left) and regions (4 SN regions) as the within-subject factors while theta phase measure was entered as the major covariate of interest. Age and global cortical thickness were entered as other covariates in this model. Although our hypothesis addresses the relationship between theta phase and cortical thickness in patients, we also tested the same linear model in healthy controls to obtain an indication of whether or not the hypothesized relationship applies only to the pathological variation in thickness occurring in patients.

Results

Demographic and clinical characteristics are shown in table 1. There was no significant difference between the two groups in terms of age, parental socio-economic status and handedness index. All subjects except one patient were predominantly right handed. Patients had significantly slower reaction times than controls (controls: mean (SD) in milliseconds=352 (45), patients: mean (SD) in milliseconds=402 (72), $t(1,36)=2.6$, $p=0.013$). The intra-individual standard deviation of reaction times (ISDRT) was significantly greater in the patient group (controls: mean (SD) in milliseconds=64 (18), patients: mean (SD) in milliseconds=94 (21), $t(1,36)=-4.5$, $p<0.001$). Patients did not differ significantly from controls in the percentage of correctly hit target tones (controls=99.35% correct hits, patients=97.62% correct hits, $t(1,36)=1.2$, $p=0.24$).

SN thickness-schizophrenia vs. controls

Repeated measures ANCOVA revealed significant main effect of diagnosis [$F(1,34)=9.83$, $p=0.004$, $ES=0.22$] and of global thickness on SN thickness [$F(1,34)=19.862$, $p=0.002$, $ES=0.37$]. Age showed

a trend to be a significant covariate in the model [$F(1,34)=3.91$, $p=0.056$, $ES=0.10$] with cortical thickness reducing with increase in age. There was no significant region X diagnosis interaction [$F(1,34)=0.83$, $p=0.37$, $ES=0.024$]. Independent t-tests of regional measures adjusted for age and global thickness revealed significant reduction in thickness at right circular superior sulcus [$t(1,36)=2.35$, $p=0.02$] and right circular anterior sulcus [$t(1,36)=3.19$, $p=0.003$]. The results are tabulated in table 2.

Contribution of phase resetting to evoked signal

In controls, T-phase significantly predicted T-mean [$F(1,18)=7.136$, $p=0.016$, $R^2=0.284$]. In schizophrenia,

T-phase did not predict the T-mean [$F(1,16)=1.079$, $p=0.314$, $R^2=0.06$] and T-mean was significantly reduced when compared to controls [$F(1,36)=9.707$, $p=0.004$] (figure 2). The difference in the beta coefficients between patients ($\beta=0.033$, $SEM=0.032$) and controls ($\beta=0.088$, $SEM=0.033$) was not statistically significant ($p=0.24$). The correlation between the phase locking and mean evoked activity in the two groups is plotted as figure 3.

Phase resetting and SN thickness in schizophrenia

Theta phase emerged as a robust predictor of SN thickness in schizophrenia [$F(1,14)=17.17$, $p=0.001$, $ES=0.55$]. Global cortical thickness, as expected, also

Table 1. Summary of the demographic data for patients and controls.

Parameter	Patients (n=18) Mean (SD)	Controls (n=20) Mean (SD)	Independent samples t test
Age	22.77 (4.88)	24 (5.00)	$t=-0.76$, $p=0.45$
Parental socio-economic status (NS-SEC)	2.55 (1.54)	1.95 (1.31)	$t=1.31$, $p=0.20$
Quick Test score	89.16	102.8	$t=-2.91$, $p=0.006$
Handedness index	10.89 (2.11)	11.60 (0.68)	$t=-1.37$, $p=0.19$
SSPI total	12.22	NA	
SSPI reality distortion	2.22	NA	
SSPI psychomotor poverty	2.66	NA	
SSPI disorganisation	0.61	NA	

NS-SEC: National statistics-socio economic status, SSPI: Signs and symptoms in psychotic illness scale, NA: Not available

Table 2. Salience Network thickness (in millimetres) adjusted for age and global mean thickness.

Brain region	Left hemisphere		Effect size	Right hemisphere		Effect size
	Controls	Patients		Controls	Patients	
	adjusted mean (SE)	adjusted mean (SE)		adjusted mean (SE)	adjusted mean (SE)	
Anterior cingulate cortex	2.41 (0.05)	2.43 (0.05)	-0.09	2.73 (0.04)	2.65 (0.04)	0.49
Short insular gyrus (anterior)	3.82 (0.05)	3.78 (0.05)	0.22	3.85 (0.05)	3.73 (0.06)	0.48
Circular sulcus anterior	2.85 (0.05)	2.86 (0.05)	-0.05	3.15 (0.06)	2.84 (0.06)	1.14**
Circular sulcus superior	2.53 (0.04)	2.47 (0.04)	0.35	2.56 (0.03)	2.44 (0.03)	0.85*

Positive values of effect sizes indicate a reduction in insular thickness in schizophrenia compared to controls. ** $p<0.001$, * $p<0.01$. SE: Standard error

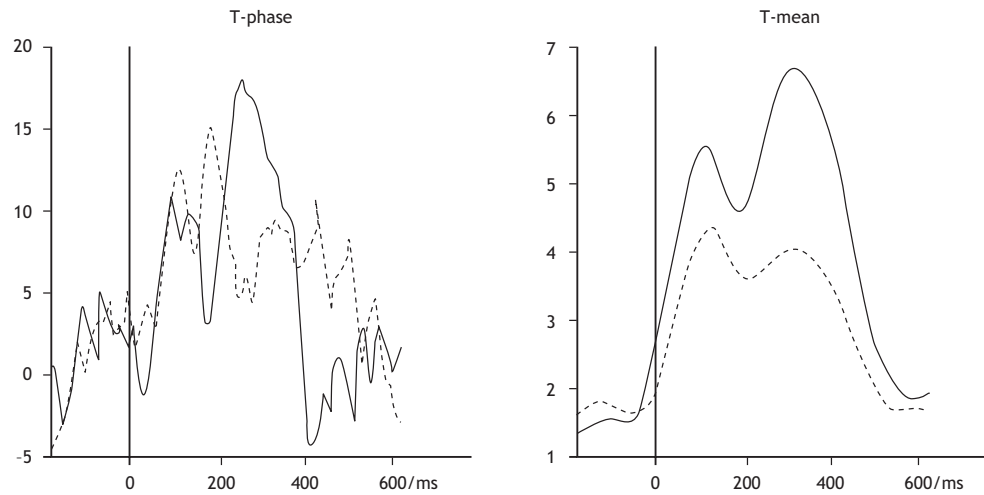


Figure 2. T-Phase and T-Mean in patients with schizophrenia and controls. Grand-average of T-mean and T-phase in the control (solid line) and patient (dashed line) group. The vertical line denotes target stimulus onset.

emerged as a significant predictor of SN thickness [F(1,14)=25.16, $p < 0.001$, ES=0.64]. Age was not a significant covariate [F(1,14)=1.61, $p = 0.23$, ES=0.10] in this model.

Significant effect was noted for regions X T-Phase interaction [F(1,14)=8.77, $p = 0.01$, ES=0.39]. Further

analysis of the parcellations on either hemisphere after controlling for mean whole brain thickness revealed that largest association of diminished thickness and phase resetting was noted in the left short insular gyrus ($r = 0.765$, $p < 0.001$) followed by the right superior circular sulcus ($r = 0.603$, $p = 0.01$) and the left

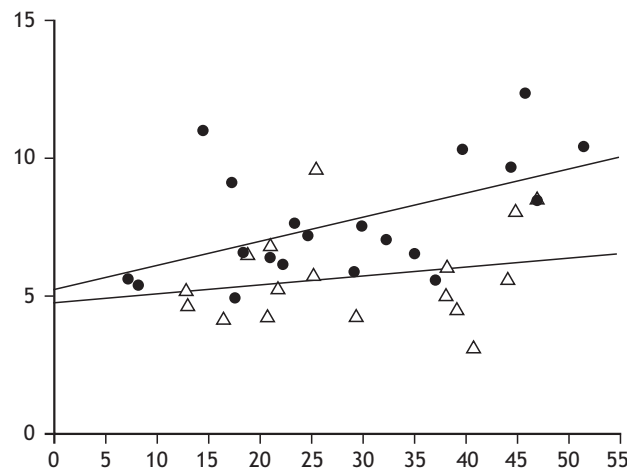


Figure 3. Relationship between Phase Reset and Evoked Activity. Scatter plot of the correlation between theta band T-phase (x-axis) and T-mean (y-axis) in the patient (triangles) and control (dots) group. (Time window: 0 to 600 ms).

superior circular sulcus ($r=0.486$ $p<0.05$). A trend towards significant correlation was seen in the right short insular gyrus ($r=0.448$ $p=0.07$). Neither left nor right anterior cingulate showed significant correlation in the post-hoc tests (left anterior cingulate $r=0.11$ $p=0.67$, right anterior cingulate $r=0.002$ $p=0.99$). Effect sizes (Pearson's correlation coefficients) from the post-hoc analysis are shown in figure 4.

In healthy controls, theta phase was not a significant predictor of the SN thickness [$F(1,16)=0.525$, $p=0.48$, $ES=0.03$].

Discussion

Using MRI morphometric analysis of cortical thickness, we have firstly shown that there is a significant loss of thickness of regions that constitute the Salience Network in patients with schizophrenia. Using EEG recording of auditory oddball target detection task we have also shown that while in healthy controls, the expected relationship be-

tween phase resetting and evoked electrical activity is observed, in schizophrenia the theta phase resetting is a weak predictor of the activity evoked by attending to a target stimulus, though the difference between the groups did not reach statistical significance. Finally, bringing together the EEG oscillatory analysis and the MRI structural analysis, we have shown that in patients with schizophrenia the grey matter reduction in the Salience Network is associated with the inefficient phase resetting of theta oscillations.

Salience network in schizophrenia

We have identified a significant reduction in the grey matter thickness of regions constituting the Salience Network in patients as predicted. This reduction is more pronounced for the insular regions on the right hemisphere. Our finding is broadly consistent with the meta-analyses of VBM studies showing that the most prominent grey matter deficits in schizophrenia are in bilateral insula and ACC.^{1,2} Studies using manual tracing or parcellation tech-

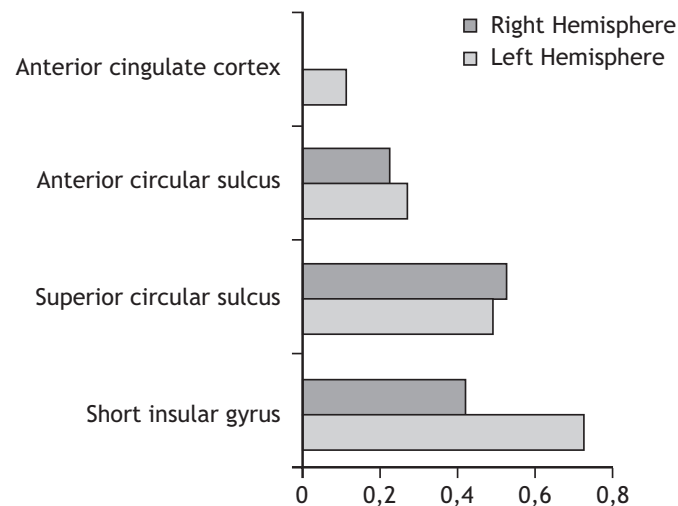


Figure 4. SN Thickness and Phase Reset. Pearson's correlation coefficients between regional thickness measures across the four parcellations of the Salience Network adjusted for global thickness and the frontal theta phase resetting measure (T-phase) in patients with schizophrenia. Statistically significant associations were present for right and left superior circular sulcus and left short insular gyrus. A trend towards positive correlation was seen in right short insular gyrus.

niques have generally concurred with the finding of grey matter reduction in the insula despite some inconsistencies (see Palaniyappan and Liddle³ for a review).

Despite numerous investigations establishing the importance of ICNs in healthy individuals, only few have explored them in schizophrenia.⁴⁰ Accumulating evidence indicates that patients with schizophrenia and their relatives exhibit difficulties in deactivating the default network during working memory tasks, resulting in tonic hyperactivation of the default network.⁴¹ Indirect evidence for involvement of various regions that constitute the salience network during attentional tasks in schizophrenia comes from odd-ball experiments in fMRI¹³ and EEG.⁴² More recently, using Independent Component Analysis of fMRI during somatosensory stimulation, White et al⁴³ have demonstrated a significant loss of the SN activation and associated DMN deactivation during perceptual processing in patients with schizophrenia.

Phase resetting

Our data shows that in healthy controls, theta phase resetting strongly predicts evoked activity. Phase resetting is a promising neurophysiological candidate for effective transmission of information regarding salience of environmental stimuli.⁴⁴ A significant portion of variability in signal detection is ascribed to the oscillatory phase preceding a stimulus.²³ Phase resetting has been shown to be a mechanism of optimising the processing of incoming information.⁴⁵ In addition, Lakatos et al using intracortical field potential recording in macaques have recently shown a direct effect of phase resetting in supramodal attentional control.²⁴ Resetting ongoing oscillatory phase to an "ideal phase" upon presentation of salient environmental stimuli may prepare various cortical regions to be in an optimum receptive state for cognitive processing. Phase resetting will tend to establish a consistent relationship between the phase of ongoing oscillations and the additive neural activity elicited by the stimulus. Depending on whether this relationship is one of mutual reinforcement or antagonism, the net amount of neural activity in a particular brain region might be either increased or decreased. Hence, while some regions are "deactivated", some others

may be "activated". Thus phase resetting may act as a high-level cognitive control mechanism reinforcing synchronous activity in brain regions required for processing the stimulus while deactivating (or switching off) cortical nodes that might interfere with the processing of current stimulus. It is worth noting that a reduction in phase resetting of low frequency oscillations has previously been reported in patients with schizophrenia.^{25,28} Given the role of phase resetting in attentional control, these abnormalities are likely to be associated with the cognitive deficits noted in schizophrenia.

Insula and salience detection

We have shown that theta phase resetting is proportionate to the thickness of Salience Network in schizophrenia. This relationship is more pronounced with insular cortex than to anterior cingulate cortex. The role of insula in salience detection and switching access between brain networks has recently been reviewed by Menon and Uddin.⁴⁶ To facilitate the description of the function of the salience network, we have introduced the concept of proximal salience.³ External or internal (bodily) events attain proximal salience when they generate a momentary state of neural activity within the salience network that results in updating of expectations and, in some cases, initiation or modification of action. To our knowledge, the physiological mechanism behind the switching ascribed to insula is hitherto unexplored. Our data shows that inefficient phase resetting of frontal theta oscillatory activity is related to abnormalities in insular thickness. This suggests that insula could act as a phase regulator that enables switching between the relevant networks via direct modulation of theta oscillations. Shulman et al⁴⁷ showed that insula, along with other regions in the SN, is highly likely to be the control region that modulates attentional shift to unexpected stimuli.

We have previously shown that the structure of the SN is related to the symptom burden in schizophrenia.^{48,49} Given that salience dysregulation is a key feature of reality distortion seen in schizophrenia, our current findings reinforce our previous proposition that insula plays a central role in generation of psychotic symptoms.³ Further, the absence of a significant relationship between theta phase and SN

thickness in healthy controls suggests that the relationship observed in patients is due to pathological variation in the grey matter of the SN.

Limitations

Our study sample is comprised entirely of males. Gender differences in brain structure have been shown though the effect of such differences on information processing deficits seen in schizophrenia remains unclear. All of our patients were medicated with antipsychotics at the time of participation. The effect of antipsychotic on brain structure is debatable. The most robust finding is increased basal ganglia volume, while there is conflicting evidence regarding other brain regions.⁵⁰ The relationship between antipsychotics and the brain oscillatory activity is currently unclear, though evidence from meta-analysis of P300 studies suggests that the antipsychotic does not account for reduced evoked

activity.⁵¹ A decrease in evoked low frequency oscillations has been noted in both medicated patients with schizophrenia and unmedicated siblings of the patients.^{52,53} This suggests that medications cannot fully explain theta oscillatory abnormalities noted in schizophrenia. While our study focused upon the Salience Network, we cannot exclude the possibility that abnormalities in other brain regions also contribute to impaired phase resetting.

Conclusion

Although several studies have investigated separately the deficits in insular grey matter, oscillatory activity, and attentional salience in schizophrenia, this is the first study bringing together these findings. Present results show that abnormalities of theta phase resetting and hence oscillatory synchrony in schizophrenia could be mediated by the insula, which forms the core of the intrinsic salience network.

Πάχος φλοιού και επαναρύθμιση της φάσης ταλάντωσης: Προτεινόμενος μηχανισμός δυσλειτουργίας του διακριτικού δικτύου στη σχιζοφρένεια

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Η σχιζοφρένεια χαρακτηρίζεται τόσο από ηλεκτροφυσιολογικές ανωμαλίες όσο και από σταθερές αλλαγές στη δομή της φαιάς ουσίας του φλοιού. Εντούτοις, η σχέση μεταξύ των δύο αυτών παρατηρήσεων είναι σε μεγάλο βαθμό άγνωστη. Οι δομικές μεταβολές που αναφέρονται στη σχιζοφρένεια περιλαμβάνουν μείωση του όγκου της φαιάς ουσίας, του πάχους και της επιφάνειας του φλοιού σε διάφορες περιοχές, πιο συχνά δε στη νησίδα και τον φλοιό του πρόσθιου προσαγωγίου. Αυτές οι δύο περιοχές αποτελούν ένα εγγενές κύκλωμα του εγκεφάλου που είναι γνωστό ως «Διακριτικό Δίκτυο» (Salience Network) το οποίο παίζει βασικό ρόλο στην επεξεργασία ερεθισμάτων. Η επεξεργασία ερεθισμάτων προκαλεί δραστηριότητα στο ηλεκτροεγκεφαλογράφημα (EEG). Η επαναφορά της φάσης των συνεχιζόμενων ταλαντώσεων συμβάλλει σε αυτήν την πρόκληση δραστηριότητας. Οι νευρικές ταλαντώσεις παίζουν κείμερο ρόλο στην εγκεφαλική επιστράτευση κατά τη διάρκεια νοητικών δοκιμασιών, και αλλαγές στη φάση της ταλάντωσης μπορούν να τροποποιήσουν την ευερεθιστότητα.

τα του φλοιού και τη μετάβαση μεταξύ διαφόρων νοητικών καταστάσεων. Σε επίπεδο δικτύου, αυτή η μετάβαση ή αλλαγή θεωρείται ότι πραγματοποιείται από το Διακριτικό Δίκτυο. Στην παρούσα μελέτη, διερευνήθηκε η σχέση μεταξύ του πάχους του φλοιού του Διακριτικού Δικτύου (μέτρηση με μαγνητική τομογραφία) και του βαθμού της επαναρύθμισης της φάσης που παρατηρήθηκε κατά τη διάρκεια μιας «δοκιμασίας παραδοξότητας» (oddball task-μετράται με HEG) σε 18 ασθενείς με σχιζοφρένεια υπό θεραπεία και σε σταθερή κλινική φάση, και 20 υγιείς μάρτυρες αντίστοιχης ηλικίας και φύλου. Καταγράψαμε μια μέτρηση της μερικής επαναρύθμισης της φάσης μετά από ερέθισμα, και μια δεύτερη μέτρηση που εκπροσωπεί τη μέση προκλητή δραστηριότητα, χρησιμοποιώντας τις μεθόδους που έχουν προτείνει οι Martinez-Montes. Χρησιμοποιώντας την ανάλυση των μαγνητικών τομογραφιών, πρώτα δείξαμε ότι υπάρχει σημαντική μείωση στο πάχος του φλοιού σε περιοχές που απαρτίζουν το Διακριτικό Δίκτυο στη σχιζοφρένεια. Η ανάλυση των ηλεκτροεγκεφαλογραφημάτων αποκάλυψε ότι στους υγιείς μάρτυρες, ενώ παρατηρείται η αναμενόμενη σχέση μεταξύ της επαναρύθμισης της φάσης και της προκλητής ηλεκτρικής δραστηριότητας, αντιθέτως στους ασθενείς με σχιζοφρένεια η επαναφορά της φάσης θα είναι ασθενής προγνωστικός δείκτης της δραστηριότητας που προκαλείται από την προσοχή σε ένα ερέθισμα-στόχο, αν και η διαφορά μεταξύ των ομάδων δεν είχε στατιστική σημαντικότητα στο παρόν δείγμα. Επιπροσθέτως, στους ασθενείς με σχιζοφρένεια το μειωμένο πάχος του Διακριτικού Δικτύου συσχετίζεται με την αναποτελεσματική επαναφορά της φάσης των ταλαντώσεων θ. Τα ευρήματά μας υποδηλώνουν ότι η μείωση της φαιάς ουσίας που παρατηρείται στο Διακριτικό Δίκτυο σε ασθενείς με σχιζοφρένεια έχει σημαντικές λειτουργικές συνέπειες. Ειδικότερα, το δομικό ελάττωμα στη νησίδα που παρατηρείται στη σχιζοφρένεια είναι πιθανόν να συνδέεται με λιγότερο αποδοτική επιστράτευση των κυκλωμάτων του εγκεφάλου για την επεξεργασία πληροφοριών. Αυτό συνεπάγεται έναν πιθανό μηχανισμό με τον οποίο διαταραχές στο εγγενές Διακριτικό Δίκτυο μπορούν να οδηγήσουν σε μια γενική διαταραχή στη διακριτική λειτουργία στη σχιζοφρένεια.

Λέξεις ευρετηρίου: Διακριτικό δίκτυο, επαναφορά φάσης, ταλαντώσεις, νησίδα, προσαγωγή.

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