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Neural synchrony in patients with a first episode of schizophrenia: tracking relations with grey matter and symptom profile

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Background: Although schizophrenia has been characterized by disruptions to neural synchrony, it remains unknown whether these disturbances are related to symptoms and loss of grey matter. We examined relations between 40 Hz Gamma band synchrony and grey matter in patients with schizophrenia at first episode and after 2.5 years. **Methods:** From an initial recruitment of 35 medicated patients with a first episode of schizophrenia, 25 patients completed clinical and oddball task-elicited Gamma synchrony within 3 months of health service contact and again after 2.5 years, 23 completed magnetic resonance imaging (MRI) at these time points, and 13 completed all sessions. We compared patients with 35 matched healthy controls. We identified early (0–150 ms) and late (250–500 ms) peaks in Gamma synchrony locked to oddball targets, and we analyzed MRI data using voxel-based morphometry. We evaluated group and test–retest differences using repeated-measures analyses of variance. **Results:** Compared with controls, at first contact, patients with a first episode of schizophrenia showed a disruption to the laterality of early Gamma synchrony and global reduction in late Gamma synchrony, with a corresponding loss of fronto–temporal–parietal grey matter. Gamma synchrony was increased at follow-up among patients with a first episode of schizophrenia. It related negatively to further loss of grey matter, but positively to improvement in reality distortion symptoms. These relations could not be explained by medication dose. **Limitations:** Our study did not include unmedicated patients or normative follow-up testing. **Conclusion:** Gamma synchrony may track the progression of schizophrenia from first episode. An increase in Gamma synchrony over time might reflect an attempt to adapt to a progressive loss of cortical grey matter and associated changes in cognitive and emotional function.

Contexte : Bien que l'on ait caractérisé la schizophrénie comme présentant des dérèglements de la synchronisation neuronale, on ignore encore s'il y a un lien entre ces dérèglements, les symptômes et la perte de matière grise. Nous avons examiné les liens entre la synchronisation oscillatoire à 40 Hz (gamma) et la matière grise chez des patients atteints de schizophrénie, au moment de leur premier épisode et après 2,5 ans. **Méthodes :** Nous avons recruté initialement 35 patients traités pharmacologiquement pour un premier épisode de schizophrénie. De ce nombre, 25 patients ont subi des tests de synchronisation oscillatoire Gamma suscitée par l'exécution d'une tâche clinique et d'une tâche inhabituelle (protocole oddball), dans les 3 mois suivant leur première prise de contact avec les services de santé et à nouveau après 2,5 ans; 23 patients ont subi un test d'imagerie par résonance magnétique (IRM) lors de ces étapes et 13 ont subi tous les tests prévus. Nous avons comparé les patients à 35 témoins assortis en bonne santé. Nous avons repéré les pics précoces (0–150 ms) et tardifs (250–500 ms) de synchronisation gamma correspondant aux cibles du protocole oddball et nous avons analysé les résultats des IRM par morphométrie voxel à voxel. Nous avons évalué les différences entre les groupes et les différences test–retest à l'aide d'une analyse de variance appliquée aux mesures répétées. **Résultats :** Comparativement aux témoins, lors du premier contact

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avec les services de santé, les patients atteints d'un premier épisode de schizophrénie ont montré un dérèglement de la latéralité de la synchronisation gamma précoce et une réduction globale de la synchronisation gamma tardive, avec perte correspondante de matière grise fronto–temporo–pariétale. Au moment du suivi, la synchronisation gamma a paru amplifiée chez les patients atteints d'un premier épisode de schizophrénie. Ce phénomène a été négativement relié à une perte accrue de matière grise, mais positivement relié à une amélioration des symptômes de distorsion de la réalité. Ces liens n'ont pu être expliqués par la dose de médicament. **Limites :** Notre étude n'incluait aucun patient qui ne prenait pas de médicaments et ne prévoyait pas l'application de tests de suivi normatifs. **Conclusion :** La synchronisation gamma pourrait permettre de suivre la progression de la schizophrénie à partir d'un premier épisode. Une accentuation progressive de la synchronisation gamma pourrait traduire une tentative d'adaptation à la perte graduelle de matière grise corticale et aux anomalies des fonctions cognitives et émotionnelles qui s'ensuivent.

Introduction

The term "schizophrenia" was initially used by Bleuler[1] to refer to a disease process that produces a "splitting of the psychic functions."[2] Recent formulations have also focused on schizophrenia as a syndrome of disconnection emphasizing a failure of rapid neuronal synchronization in subcortical–cortical circuits and corresponding disruption to cognitive and emotional functions.[3–7] Converging evidence from functional neuroimaging and postmortem studies points to fundamental abnormalities in synaptic connectivity that may underlie the symptoms of schizophrenia.

Magnetic resonance imaging (MRI) has revealed evidence for progressive loss of fronto-temporal grey matter volume beginning with the first episode of schizophrenia.[8–10] Postmortem studies suggest that diminished volume, especially in the prefrontal cortex, in patients with schizophrenia may be due to a decreased amount of cortical neuropil, namely the axon terminals, distal dendrites and dendritic spines that represent the principal components of cortical synapses.[11] Evidence from postmortem research indicates that these alterations in synaptic connectivity are likely to involve γ-aminobutyric (GABA) neurons. Patients with schizophrenia have been found to have a substantial reduction in expression of presynaptic markers for the GABAergic interneurons that have specific connections for innervating pyramidal cells.[12] This reduction is particularly apparent in the frontal cortex, but also in the temporal regions.

These alterations in synaptic connectivity may directly impact the real-time synchronization of brain function in patients with schizophrenia. The mutual interaction of inhibitory GABAergic interneurons and their in-phase firing with excitatory pyramidal neurons has been proposed as the mechanism underlying Gamma synchrony:[13] the phase synchronization of neural activity in the high-frequency (40 Hz) Gamma band. Gamma synchrony has been implicated in the binding of distributed neural activity for coherent cognition in real time.[14] The important feature of this measure is the temporal coding. That is, it refers to changes in activity at 40 Hz that are not only synchronous (or coherent), but also have near zero time lag (i.e., "in phase"). Disturbances in Gamma synchronization have been observed in patients with schizophrenia at first episode[7,15] and in more chronic phases[16–19] and also in their first-degree relatives.[20] These disturbances reflect a topographical disorganization (e.g., a reduction in frontal synchrony, but an increase in parietal synchrony) associated with a loss of signal-to-noise discrimination.

Variations in frontal grey matter have been associated with Gamma synchrony in healthy individuals.[21] However, it is not yet known whether Gamma synchrony disturbances in patients with schizophrenia also vary over time and reflect contributions from progressive loss of grey matter. In healthy individuals, changes in electroencephalography have been found to parallel changes in grey matter.[22] Patients with schizophrenia show a dissociation between enhanced electroencephalography activity and progressive loss of grey matter, which might reflect disturbances in neural synchrony.[23]

In the present study, we used a test–retest design to examine the progression of Gamma synchrony from the first episode of schizophrenia to follow-up 2.5 years later. We also sought to examine the contribution of corresponding changes in grey matter. Drawing on previous findings,[18,19] it was predicted that patients experiencing a first episode would show a progressive loss of frontal and temporal grey matter, particularly on the left side, and that this loss would be associated with a similarly progressive loss of Gamma synchrony. Given the evidence that abnormalities in Gamma activity vary with symptom profile in chronic but not first episodes of schizophrenia, we investigated whether symptoms vary with the progression of Gamma synchrony and changes in grey matter.

Methods

Design

We performed clinical assessments, electroencephalography and MRI testing at both baseline and follow-up testing sessions at an interval of 28.2 (standard deviation [SD] 6.6) months.

Study population

We recruited 35 patients experiencing their first episodes of schizophrenia as part of the Western Sydney First Episode Psychosis project, headed by A.W.F.H.[24] Testing occurred within 3 months of the first presentation to mental health services. Schizophrenia was diagnosed using *Diagnostic and statistical manual of mental disorders*, fourth edition, (DSM-IV) criteria[25] and a structured interview (SCID, Research version).[26] A consensus of 3 senior psychiatrists, at least 2 independent of the study, confirmed the diagnosis. We noted whether patients were taking medication.

Follow-up testing occurred after 24–36 months. Of the patients recruited into the study, 25 completed Gamma synchrony testing at first contact and follow-up, and 23 completed MRI testing at both sessions (reasons for noncompletion are available online in Appendix 1 at www.cma.ca/jpn). There were 13 patients who completed both Gamma synchrony and MRI testing for both sessions.

We used the Positive and Negative Syndrome Scale[27] to assess symptoms at baseline and follow-up. Inter-rater intraclass reliability for 3 raters with formal Positive and Negative Syndrome Scale training was appropriately high (0.81). Following previously published procedures,[28] we summed individual symptom ratings (at baseline and follow-up) to form these dimensions. We assessed medication dosage in chlorpromazine equivalent units[29] at both testing sessions.

Using a structured interview and questionnaire that included mini-mental status examination items, we screened healthy controls for the presence of axis 1 symptoms according to DSM-IV criteria; current or past history of substance dependence; exposure to electroconvulsive therapy within the 6 months preceding the study; mental retardation; neurologic disorder, including epilepsy; and a history of head injury causing loss of consciousness for at least 1 hour. We matched these participants to patients on age (within 2 yr), IQ estimate and handedness for both Gamma synchrony and MRI baseline testing sessions. We tested them on the same equipment as patients with a first episode of schizophrenia.

The Sydney West Area Health Service Human Research Ethics Committee approved this study, and each participant provided written informed consent.

Behavioural task

We acquired electroencephalographic data, from which we extracted Gamma synchrony indices, during a standard auditory oddball task. This task captures the ability to selectively orient and attend to a task-relevant signal (infrequent high-pitched oddball tones) and ignore a task-irrelevant noise stimulus (frequent low-pitched standard tones). Although both oddball and standard stimuli elicit an N100-P200 complex (peaking 100–200 ms poststimulus), oddball tones are differentiated by a comparatively larger P300 complex (peaking 300 ms), reflecting selective orientation. Correspondingly, both oddball and standard stimuli elicit early peaks in Gamma synchronization (within 150 ms), but only oddball targets produce a peak in later synchronization (200–500 ms).[30]

We presented a series of high-pitched (1500 Hz) target tones pseudorandomly (with the constraint that there were no successive target stimuli) among lower pitch (1000 Hz) nontarget tones. The tones were presented binaurally through stereo headphones via computer with the following specifications: 50 ms duration, 10 ms rise and fall time and 80 dB above the hearing threshold (determined individually). Of these tones, 85% were nontargets and 15% were targets. Interstimulus interval was 1.3 seconds. We instructed participants to ignore nontarget tones and attend and respond to target tones as quickly and accurately as possible by pressing a button with the first finger of each hand (to counterbalance for possible motor effects). We continued recording until participants identified 40 target tones correctly. We asked participants to refrain from smoking or drinking caffeine for 3 hours before the recording session to control for these effects on electroencephalography data.

Gamma synchrony data acquisition

We acquired electroencephalography recordings using a SynAmps (Compumedics Neuroscan) DC system with an electrode cap. We recorded data from 19 sites according to the international 10–20 system (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, P3, Pz, P4, T3, T4, T5, T6, O1, O2) and referenced them to an average of electrodes at A1 and A2 sites. We recorded horizontal eye movements with electrodes placed 1 cm lateral to the outer canthus of each eye; we recorded vertical eye movements with electrodes placed 3 mm above the middle of the left eyebrow and 1 cm below the middle of the left bottom eyelid. The digitization rate was 250 Hz, and impedence was less than 5 kohms. We corrected data on ocular artifact offline based on the algorithm by Semlitsch and colleagues[31] and Gratton and colleagues.[32] We confirmed the removal of eye blink and eye movement artifact by visual inspection of the data. We also filtered the specific frequency of 50 Hz, since this is the frequency at which there is potential interference in electrical systems in Australia. But, since we filtered only 50 Hz, this did not affect the frequency bins of interest to our study.

Gamma synchrony data reduction

We quantified phasic peaks in Gamma synchrony from electroencephalography recordings for correctly identified target trials using a previously established protocol.[30]

We first detrended single trial data for oddball target stimuli by subtracting the line of best fit, centred at stimulus presentation. To determine frequency bins, we applied fast Fourier transformation at each time sample using a Welch window with a 256-ms, 64-sample window length.

We quantified the phase synchronization of Gamma activity within the 37.15–41.06 Hz frequency bin for each of the target trials across 6 regions of interest (ROIs) relevant to areas of grey matter reduction in patients with schizophrenia: the left frontal (Fp1, F3, F7), right frontal (Fp2, F4, F8), left centro-temporal (C3, T3, T5), right centro-temporal (C4, T4, T6), left parieto-occipital (CP3, P3, O1) and right parieto-occipital (CP4, P4, O2) regions. We computed circular variance from the phase estimates of the electrode sites making up each region. This measure is a normalized index ranging from 0 to 1 that is independent of the amplitude of response. Like a correlation coefficient, it therefore has no associated units of measurement. Unlike a coherence estimate, circular variance provides a measure of the phase-locking across multiple (rather than 2) sites. For ease of interpretation, we calculated phase synchrony as the inverse of circular variance (or 1 minus circular variance), such that a value of 1 represented maximum synchrony.

This procedure produced a time series of Gamma phase synchronization for each region, which could be plotted to

show the degree of phase locking across time. We averaged these time series across target trials for each participant. On the basis of previous evidence showing the separation of 2 peaks in synchronization for the oddball task, we scored peak magnitude for early "evoked" Gamma synchrony (0–150 ms) and late "induced" Gamma synchrony (200–500 ms) for each region. Given the length of the Welch window centred at stimulus onset, the tail of the early peaks in Gamma synchrony could commence within the period –100 ms. Scoring was undertaken relative to a prestimulus baseline by subtracting the baseline average of –450 to –150 ms from each time sample; this baseline average allowed for the length of the Welch window centred at stimulus onset. Evoked synchrony has been related to both target and nontarget stimuli, consistent with early sensory analysis. The induced Gamma peak occurs only for task-relevant targets, and is associated with reaction time for these stimuli, suggesting that it represents synchronization associated with stimulus context evaluation.[33]

Methodologic issues in Gamma synchrony

To provide a broader context for interpretation of synchrony data, we considered several methodologic issues, including previous studies indicating that electromyography and volume conduction are unlikely to contribute to the current method used to quantify synchrony. In addition, we demonstrated that oddball-elicited event-related potentials showed the expected differences for patients with a first episode of schizophrenia compared with controls, and we used time-frequency plots (across the Gamma band 29.33–48.88) to confirm that these differences were particularly apparent within the 37.15–41.06 Hz frequency bin (Appendix 1).

MRI data acquisition

At baseline and follow-up, we performed a single T_1-weighted volumetric magnetization-prepared rapid-acquisition gradient echo structural scan using a Siemens 1.5-Tesla Vision Plus system at Westmead Hospital, Sydney, Australia. We obtained images coronally with the following parameters: repetition time 9.7 ms, echo time 4 ms, inversion time 200 ms, flip angle 12°, field of view 256 mm, 250 slices, voxel size 1 mm^3. Using phantom data, we calibrated the scanner weekly during the testing interval to control for scanner drift. We did not modify the scanner between testing sessions.

MRI data reduction

We processed both baseline and follow-up images using SPM2 (Wellcome Trust Centre for Neuroimaging) running on MATLAB 6.5 (MathWorks) and a voxel-based morphometry protocol, which had been established previously.[34] We spatially normalized images to the ICBM 152 template (Montreal Neurological Institute), which approximates Talairach space, in 2 steps. We first estimated the optimal 12-parameter affine transformation (3 translations, 3 rotations, 3 zooms and 3 shears) for matching images to the template, and we then used a linear combination ($7 \times 8 \times 7$) of smooth spatial basis functions to model global nonlinear shape differences. We resliced normalized images with 1.5 mm^3 voxels; segmented them into grey matter, white matter and cerebrospinal fluid probability maps; and stripped them of extracerebral voxels. We based segmentation on a cluster analysis method that accounted for each voxel's signal intensity, together with an a priori expectation of the anatomic location of the different tissue types. Voxel probability values in segmented images were modulated with the Jacobian determinants derived from the spatial normalization, to adjust for any growth or shrinkage due to normalization. We smoothed the processed grey matter images with a Gaussian kernel of 12-mm full-width at half-maximum. We then parcellated resulting grey matter images for baseline and follow-up into previously established ROIs in Talairach space,[22] using the following automatic anatomic labelling masks for both left and right hemispheres:[35] frontal, temporal, parietal and occipital cortices (see Appendix 1 for definitional boundaries).

Statistical analysis

We used mixed-design repeated-measures analysis of variance (ANOVA) to analyze group differences in Gamma synchronization (37.15–41.06 Hz) and grey matter volume. In these analyses, group was the between-subject factor, brain region (frontal, temporal and parieto-occipital ROIs) and laterality (left v. right hemisphere) were the within-subject factors and sex was the covariate. We also confirmed that age did not correlate significantly with Gamma synchrony or MRI. We used planned contrasts to compare groups on each measure, with an a priori α level of 0.05.

To analyze first contact to follow-up changes on Gamma synchronization (n = 25) and grey matter volume (n = 23), we performed within-subject repeated-measures ANOVA with time, region and laterality as within-subject factors and sex as a covariate. We used planned contrasts to assess changes from first contact to follow-up for each measure, with an α level of 0.05. We used a second set of repeated-measures ANOVA to assess changes in symptoms (Positive and Negative Syndrome Scale ratings) for patients with schizophrenia within Gamma synchrony and MRI cohorts. For these cohorts, we performed Pearson bivariate correlation analyses to examine relations between change in symptoms and change in both Gamma synchrony and grey matter. We also explored the correlation between change in Gamma synchrony and change in grey matter for patients with a first episode of schizophrenia who completed all testing sessions. Given the working hypotheses for these correlations, the α level was 0.017 (corrected for 3 ROIs, with left and right sides as repeated observations).

Results

Study population

Of the 35 patients enrolled in the study, 25 were young men or adolescent boys and 10 were young women or adolescent girls. Their mean age was 19.5 (SD 3.3) years, and their mean premorbid IQ was 101.2 (SD 11.1), as assessed by the Wide

Range Achievement Test.[36] The mean duration of untreated psychosis was 4 (SD 5.4) months. Of the 35 patients, 19 were taking risperidone, 15 olanzapine, 1 clozapine, 1 quetiapine, and 3 were unmedicated. Table 1 summarizes clinical and demographic characteristics.

We enrolled 35 healthy controls. Of these we tested 23 (18 young men/adolescent boys and 5 young women/adolescent girls) for Gamma synchrony. Their mean age was 18.8 (SD 3.3) years, 21 were right-handed and their mean IQ estimate was 105.0 (SD 9.2). We performed MRI for 26 controls (15 young men/adolescent boys and 11 young women/adolescent girls). Their mean age was 21.9 (SD 4.4) years, 25 were right-handed and their mean IQ estimate was 103.1 (SD 8.3).

Behavioural data

At first contact, patients with a first episode of schizophrenia had significantly slower reaction time for accuracy of oddball target identification compared with controls (t_{44} = 3.892, $p < 0.001$). The mean reaction time was 368 (SD 91) ms for patients, and 310 (SD 43) ms for controls. Patients showed no significant change in reaction time at follow-up testing (mean 359, SD 102 ms, $p = 0.64$).

Gamma synchrony

The mean number of correct trials was 39.2 (SD 0.50) for patients and 39.8 (SD 0.22) for controls. Our analysis of fast Fourier transformation at each time sample resulted in frequency bins centred at 31.28 (29.33–33.24) Hz, 35.19 (33.24–37.15) Hz, 39.10 (37.15–41.06) Hz, 43.01 (41.06–44.97) Hz and 46.92 (44.97–48.88) Hz within the range of the Gamma band. In healthy controls the Gamma response induced by the oddball task is most apparent in the 37.15–41.06 Hz frequency bin.[30]

First contact: patients with schizophrenia versus controls

There was a significant main effect for group for both early ($F_{1,47}$ = 5.52, p = 0.020) and late Gamma synchrony ($F_{1,47}$ = 4.441, p = 0.039), reflecting a general reduction in synchrony in patients with a first episode of schizophrenia compared with controls across the time course of 0–500 ms (Fig. 1). The mean data showed that, for early synchrony (0–150 ms), reductions were most apparent in the left temporal and bilateral parieto-occipital brain regions of patients with schizophrenia. For late synchrony (200–500 ms), there was a partially dissociable pattern of more pronounced reductions in left-sided temporal and parieto-occipital synchrony and in bilateral frontal synchrony (Fig. 1, Fig. 2).

These group differences in Gamma synchrony did not covary significantly with reaction time.

First contact versus follow-up

Within the schizophrenia group, analyses of first contact versus follow-up revealed a 2-way time by laterality

Table 1: Demographic and clinical variables for patients with a first episode of schizophrenia who completed Gamma synchrony testing, MRI testing, or both Gamma synchrony testing and MRI*

Variable	Patient cohort; mean (SD)†		
	Gamma synchrony	MRI	Both Gamma synchrony and MRI
Demographics			
No. who completed testing	25	23	13
Age (SD) [range], yr	19.5 (3.3) [13–25]	18.2 (3.0) [13–25]	19.0 (3.4) [13–25]
Sex distribution, M/F	15/10	13/10	7/6
Handedness, R/L	20/5	20/3	11/2
Premorbid IQ	100.1 (11.1)	102.3 (10.3)	100.5 (11.2)
Baseline: clinical profile			
Duration of untreated psychosis, mo	4.2 (4.9)	3.9 (4.7)	3.6 (3.9)
Medication dosage, CPZ b	254 (206)	247 (211)	250 (225)
Psychomotor poverty	13.7 (4.9)	13.0 (4.9)	14.0 (4.6)
Disorganization	11.7 (4.7)	12.3 (4.9)	12.1 (5.4)
Reality distortion	11.7 (4.0)	11.1 (3.8)	11.7 (4.3)
Follow-up: clinical profile			
Follow-up interval, mo	30.9 (6.0)	34.0 (6.0)	32.9 (5.4)
Medication dosage, CPZ b	252 (272)	242 (277)	250 (281)
Psychomotor poverty‡	11.0 (5.2)	10.6 (5.8)	11.2 (6.0)
Disorganization§	8.5 (3.4)	8.1 (3.5)	8.6 (3.6)
Reality distortion§	8.9 (4.8)	8.7 (5.1)	8.5 (5.4)

CPZ b = chlorpromazine equivalent units; F = female; IQ = intelligence quotient; L = left; M = male; MRI = magnetic resonance imaging; R = right; SD = standard deviation.
*There were no significant differences between samples in mean age (p = 0.82), sex (p = 0.46), handedness (p = 0.70) and premorbid IQ (p = 0.86). At baseline, there were no differences in duration of untreated psychosis (p = 0.58), medication dosage in CPZ b (p = 0.76), psychomotor poverty (p = 0.91), disorganization (p = 0.61) and reality distortion (p = 0.74). At follow-up there were no differences in CPZ b (p = 0.69), psychomotor poverty (p = 0.75), disorganization (p = 0.64) and reality distortion (p = 0.77). Thus differences in samples (owing to the number of participants completing testing) were unlikely to account for the MRI and Gamma synchrony data.
†Unless otherwise indicated.
‡There was an improvement in psychomotor poverty symptoms from baseline to follow-up in patients with a first episode of schizophrenia at the trend level (p = 0.07).
§There was a significant improvement in disorganization ($p < 0.001$) and reality distortion (p = 0.003) symptoms from first contact to follow-up in patients with a first episode of schizophrenia.

interaction for early Gamma synchrony ($F_{1,22}$ = 8.093, p = 0.009), along with a 3-way time by laterality by region interaction ($F_{2,42}$ = 4.930, p = 0.012). Planned contrasts showed that there was an increase from first contact to follow-up in left-sided early Gamma synchrony ($F_{1,22}$ = 4.633, p = 0.050) that was most apparent in the left parieto-occipital region ($F_{1,22}$ = 5.455, p = 0.029) (Fig. 1).

There was also a time by laterality interaction for late Gamma synchrony ($F_{1,22}$ = 6.21, p = 0.021), which contrasts showed was due to an increase in left-sided synchrony ($F_{1,22}$ = 5.124, p = 0.039), particularly in the left temporal ($F_{1,22}$ = 5.202, p = 0.033) and left parieto-occipital ($F_{1,22}$ = 4.323, p = 0.049) regions (Fig. 1).

These changes in Gamma synchrony did not covary with changes in reaction time.

MRI analyses

First contact: patients with schizophrenia versus controls

Consistent with previous findings,[18,19] there was a significant group by laterality by region interaction ($F_{2,47}$ = 11.791, p < 0.001), reflecting a general reduction in cortical grey matter in patients with a first episode of schizophrenia compared with controls (Fig. 1). The reduction was most apparent for right temporal grey matter ($F_{1,48}$ = 3.56, p = 0.06, loss = 4.4%) compared with other regions: 2.2% in the left temporal, 1.4% in the left frontal, 1.3% in the right frontal, 0.7% in the left parieto-occipital and 1.8% in the right parieto-occipital cortices (Fig. 1).

First contact versus follow-up

Analyses of first contact versus follow-up revealed a significant progressive reduction in grey matter in patients with a first episode of schizophrenia across all brain regions, reflected in a significant main effect for time ($F_{1,23}$ = 8.675, p = 0.007). However, some regions showed a greater reduction than others, as indicated by a time by region interaction ($F_{2,46}$ = 8.661, p = 0.001) and a trend toward a time by laterality interaction ($F_{1,23}$ = 3.750, p = 0.065). Over and above the general progressive reduction in grey matter, reductions were greatest in the frontal and parieto-occipital regions compared with the temporal regions: left frontal ($F_{1,23}$ = 12.80, p = 0.002, loss = 5.2%), right frontal ($F_{1,23}$ = 7.14, p = 0.014, loss = 5%), left parieto-occipital ($F_{1,23}$ = 10.9, p = 0.003, loss = 4.9%), right parieto-occipital ($F_{1,23}$ = 5.01, p = 0.035, loss = 4.1%) and left temporal ($F_{1,23}$ = 5.20, p = 0.032, loss = 2.8%).

Relation between Gamma synchrony and grey matter

For the group of patients who completed both Gamma synchrony and MRI testing, the increase in Gamma synchrony was related to the loss of grey matter, significantly in the right temporal (r = –0.750, p = 0.003) and right parieto-

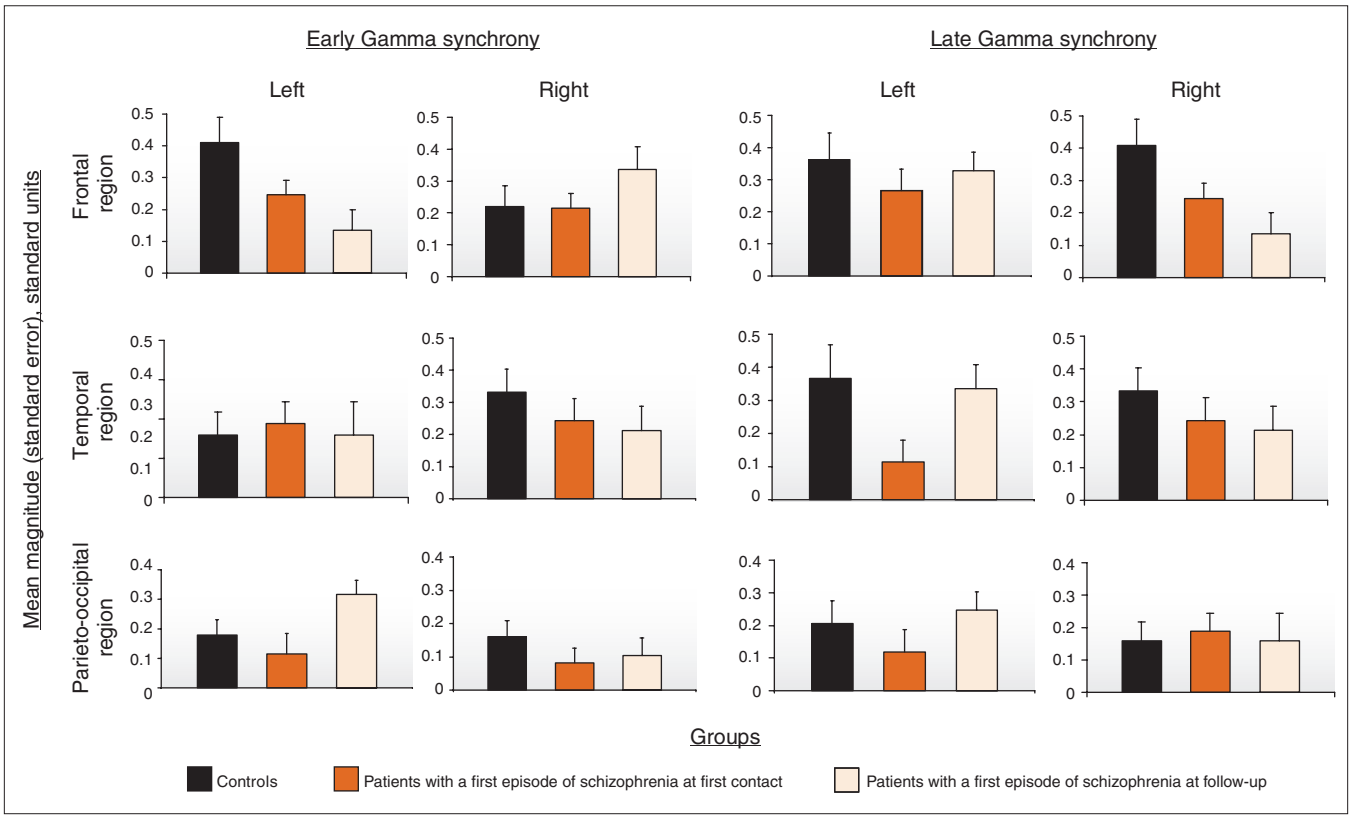

Fig. 1: Bar plots of the mean magnitude (and standard error) of early and late Gamma synchrony for patients with a first episode of schizophrenia at first contact and follow-up compared with healthy controls for left and right sides of parieto-occipital, temporal and frontal brain regions.

occipital regions ($r = -0.682$, $p = 0.010$), and at trend level in the left parieto-occipital ($r = -0.622$, $p = 0.023$) and right frontal regions ($r = -0.615$, $p = 0.025$).[22]

Clinical profile

For patients who completed Gamma synchrony testing, there was an improvement in overall symptom severity ($F_{1,23} = 12.186$, $p = 0.004$), which planned contrasts showed was due to improvements in disorganization ($F_{1,23} = 14.228$, $p < 0.001$), reality distortion ($F_{1,23} = 7.609$, $p = 0.012$) and psychomotor poverty ($F_{1,23} = 4.192$, $p = 0.048$). Similarly, for patients who completed MRI testing, there was an improvement in overall symptoms ($F_{1,24} = 13.589$, $p = 0.002$) reflected in reductions in disorganization ($F_{1,24} = 16.661$, $p < 0.001$), reality distortion ($F_{1,24} = 10.277$, $p = 0.005$) and, at trend level, psychomotor poverty ($F_{1,24} = 3.576$, $p = 0.07$) at follow-up. There was no difference in medication dosage (chlorpromazine equivalents) from first contact to follow-up for either the Gamma synchrony ($t_{23} = 0.047$, $p = 0.863$) or the MRI group ($t_{24} = 0.038$, $p = 0.915$) (Table 1).

Relation of Gamma synchrony and grey matter with clinical profile

There was a specific significant relation between improvement in reality distortion symptoms and the increase in left temporal early Gamma synchrony at follow-up ($r = -0.621$, $p = 0.006$).

On the other hand, improvement in disorganization was significantly associated with a smaller progressive loss of grey matter in the right frontal ($r = -0.492$, $p = 0.017$), left frontal ($r = -0.495$, $p = 0.016$) and right temporal ($r = -0.602$, $p = 0.002$) regions and, at trend level, in the left parieto-occipital region ($r = -0.424$, $p = 0.044$) at follow-up. We confirmed that these correlations were not affected by age or sex.

For the patient group that completed both Gamma synchrony and MRI testing, there were no significant correlations between medication dosage and change in either Gamma synchrony or grey matter volume.

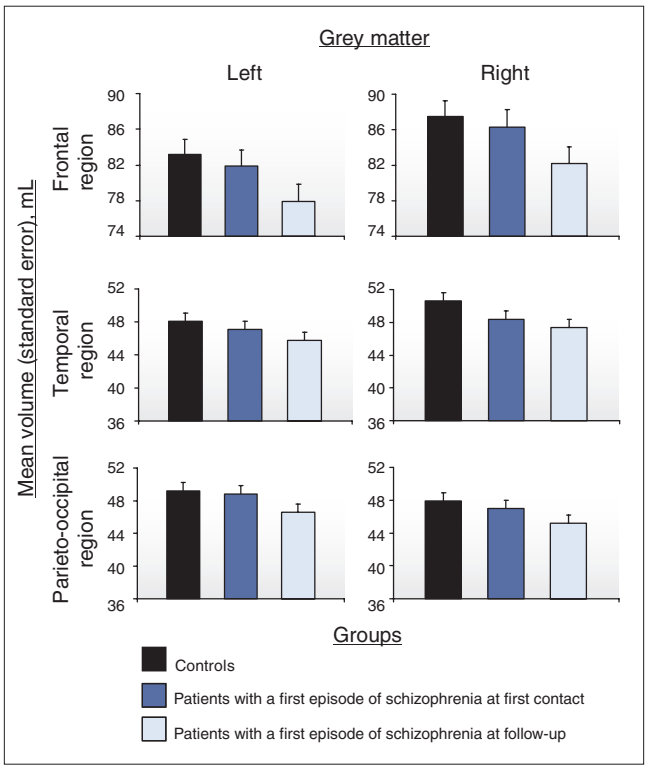

Fig. 2: Bar plots of the mean magnitude (and standard error) of grey matter volume (mL) for patients with a first episode of schizophrenia at baseline and follow-up compared with healthy controls for left and right sides of parieto-occipital, temporal and frontal brain regions, corresponding to the regions for Gamma synchrony.

Discussion

Our study provides new findings to suggest that disturbances in high-frequency neural synchrony in patients with schizophrenia may be related to loss of cortical grey matter that occurs early in the illness. At first episode, patients with schizophrenia showed a reduction in stimulus-locked Gamma synchrony compared with healthy controls over left temporal and parieto-occipital regions. At follow-up 2.5 years later, there was an increase in Gamma synchrony among patients that was related to a progressive loss of grey matter, but the patients showed improvement in symptoms of reality distortion. Although the causal chain underlying these relations is unclear at this stage, several possibilities can be examined further. The increase in Gamma synchrony might reflect the partial recovery in positive symptoms, the attempt to compensate for ongoing loss of grey matter by excessive integration of neuronal networks involved in processing salient stimuli, effects of pharmacotherapy over time, or a combination of these factors.

The disruption to the normal lateralized organization of early (sensory-related) Gamma synchrony and a global reduction to later (context-related) Gamma synchrony observed at the first episode of schizophrenia in the present study is consistent with previous reports.[15,17–19] Similarly, our finding that cortical grey matter was reduced from the first episode of schizophrenia, particularly in the temporal cortex, is consistent with previous evidence using voxel-based morphometry.[37,38] A new observation was the opposing changes in Gamma synchrony and grey matter in schizophrenia at the 2.5-year follow-up: while synchrony increased over left-sided temporal and parieto-occipital regions, grey matter progressively decreased in the left frontal and parieto-occipital cortices. The increase in left temporal synchrony was specifically correlated with the progressive contralateral loss of fronto-temporal and bilateral parieto-occipital grey matter.

These changes in synchrony and grey matter in patients with schizophrenia were also related to some aspects of symptomatology. The increase in left temporal synchrony over time was related to the improvement in reality distortion symptoms. It is possible that these relations reflect an attempt to compensate for the detrimental effects of progressive grey matter loss on cognitive and emotional functions through a state of excessive synchronization of neural

systems involved in selective processing of task-relevant stimuli. This proposal is consistent with evidence in healthy controls that poorer cognitive performance relates to higher Gamma synchrony.[39]

In previous research, progressive reductions in grey matter have also been related to opposing changes in electroencephalography power in patients with a first episode of schizophrenia compared with healthy controls.[22] Although healthy adolescents show a reduction in both brain electrical activity and grey matter over 2 years, consistent with normal neural pruning, patients with a first episode of schizophrenia show a divergent trend toward higher activity with a significantly more pronounced loss of grey matter in spite of treatment with antipsychotic medication and improvement in symptoms. Given that electrical activity is a function of synchrony as well as the number of active synapses, this divergent trend in schizophrenia may reflect a disruption in the normal mechanisms of neural synchrony under conditions of excessive synaptic loss. Gamma synchrony is thought to involve a mutual interaction of inhibitory GABAergic and excitatory glutamatergic neural action. As such, a progressive removal of synapses (entire neurons or selected dendrites and axon terminals) reflected in the loss of grey matter in patients with schizophrenia may disrupt inhibitory GABAergic action and produce a complementary excess of excitatory action.

Consistent with theoretical models of schizophrenia, Gamma synchrony may be a marker of the pathophysiological progress of the illness from first episode. A loss of stimulus-elicited synchrony at the onset of schizophrenia is consistent with theories focusing on the disruption to coherent thought and feeling.[1,3] An increase in synchrony with the unfolding of the illness might reflect attempts to compensate for the loss of coherent function and its exacerbation due to progressive grey matter loss. Nonetheless, previous cross-sectional studies have observed a positive relation between severity of disorganization and reality distortion symptoms and abnormal increases in both Gamma synchrony and Gamma power in patients with chronic schizophrenia.[16,40] Thus with a chronic course of schizophrenia and active symptomatology, a more persistent disruption to Gamma synchrony may occur.

Limitations

There are limitations to the study, requiring further research to replicate and extend the findings. First, there were 13 patients who completed both Gamma synchrony and MRI testing for both sessions. Although this represents an important drop-out rate for the combined longitudinal testing, the final sample was nonetheless of a size equivalent to many previous psychophysiology and neuroimaging studies. We tested factors that might have differed among patients who did or did not complete the combined testing that would limit the generalizability of our results. However, results of our ANOVA and χ^2 analyses showed no significant differences among these groups in terms of demographics (age, premorbid IQ, handedness), duration of untreated psychosis, medication dosage, follow-up interval or symptom severity.

It would be important to address the lack of follow-up normative testing in the present study to understand the inverse relations between Gamma synchrony and grey matter in schizophrenia in direct comparison to the normative context. Evidence to date suggests that healthy adolescents and young adults show much smaller changes in electroencephalography and grey matter measures over a 2.5-year period of follow-up similar to that in our study,[22] which would not account for the changes in schizophrenia. Correspondingly, cross-sectional research reveals minimal changes in Gamma synchrony over age.[39] Verification of the present findings are also warranted in larger samples of patients who have completed both Gamma synchrony and structural scanning.

Although there was no linear association with medication dosage in our study, definitive evidence would come from unmedicated patients. There is evidence that Gamma activity may be suppressed by typical antipsychotics in healthy controls and may vary with typical versus atypical antipsychotics in patients;[41,42] however, these findings do not take into account the differences between patients with schizophrenia and healthy controls.

Additionally, convergent evidence for synchrony–brain structure relations might be sought using complementary methods for quantifying neural integration, such as nonlinear electroencephalography methods, intertrial coherence and functional MRI connectivity.[43–45] It would also be important to examine whether the present findings are specific to the high frequency Gamma range, or whether they manifest in lower frequencies associated recently with feature independent cognitive functions.[46,47] To further elucidate the functional significance of the findings, investigation into their contribution to cognitive and emotional phenotypic markers and functional outcomes in schizophhrenia[48] is warranted.

These avenues of future research notwithstanding, our study provides promising early evidence for the value of Gamma synchrony as an electrophysiological marker that may track the progression of schizophrenia.

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Contributors: Drs. Williams and Gordon designed the study. All authors acquired the data, reviewed the written article and gave final approval for publication. Drs. Williams, Whitford, Gordon and Brown analyzed the data.

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