# Aberrant Current Source-Density and Lagged Phase Synchronization of Neural Oscillations as Markers for Emerging Psychosis

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*Background:* Converging evidence indicates that neural oscillations coordinate activity across brain areas, a process which is seemingly perturbed in schizophrenia. In particular, beta (13-30 Hz) and gamma (30–50 Hz) oscillations were repeatedly found to be disturbed in schizophrenia and linked to clinical symptoms. However, it remains unknown whether abnormalities in current source density (CSD) and lagged phase synchronization of oscillations across distributed regions of the brain already occur in patients with an at-risk mental state (ARMS) for psychosis. *Methods:* To further elucidate this issue, we assessed resting-state EEG data of 63 ARMS patients and 29 healthy controls (HC). Twenty-three ARMS patients later made a transition to psychosis (ARMS-T) and 40 did not (ARMS-NT). CSD and lagged phase synchronization of neural oscillations across brain areas were assessed using eLORETA and their relationships to neurocognitive deficits and clinical symptoms were analyzed using linear mixed-effects models. *Results:* ARMS-T patients showed higher gamma activity in the medial prefrontal cortex compared to HC, which was associated with abstract reasoning abilities in ARMS-T. Furthermore, in ARMS-T patients lagged phase synchronization of beta oscillations decreased more over Euclidian distance compared to ARMS-NT and HC. Finally, this steep spatial decrease of phase synchronicity was most pronounced in ARMS-T patients with high positive and negative symptoms scores. *Conclusions:* These results indicate that patients who will later make the transition to psychosis are characterized by impairments in localized and synchronized neural oscillations providing new insights into the pathophysiological mechanisms of schizophrenic psychoses and may be used to improve the prediction of psychosis.

*Key words:* schizophrenia/at-risk mental state (ARMS)/resting state/EEG

## Introduction

Converging evidence suggests that an impaired dynamic coordination of activity across distributed brain areas underlies the cognitive and behavioral abnormalities that characterize psychosis.[1–4] Neural oscillations coordinate distributed activity through phase synchronization,[5] and patients with schizophrenia display altered neural oscillations, particularly in the beta (13–30 Hz) and gamma (30–50 Hz) frequency bands.[3,6] Together, these findings suggest that alterations in higher frequency oscillations and their phase synchronization may disrupt coordinated activity across distributed cortical areas, thereby leading to the formation of psychotic symptoms and cognitive impairments.

Gamma oscillations are strongly associated with the integration of cognitive information[7–9] and have been shown to be consistently perturbed in patients with schizophrenia.[3,10,11] Interestingly, both an elevated and reduced gamma activity has been reported in patients with schizophrenia.[12] However, an increase has consistently been found in unmedicated patients experiencing positive symptoms (such as hallucinations and delusions), while the reverse is apparent in those suffering from negative symptoms (such as social withdrawal, lack of motivation, and flat affect).[11,12] Although both gamma and beta oscillations synchronize with enhanced precision over small distances, the beta oscillations have been shown to be particularly important in modulating long-range synchronization,[13,14] which is the interaction among widely distributed neocortical regions. For instance, the phase synchronization of beta oscillations between extra-striate areas[15] and between temporo-parietal areas[16] have been shown to mediate attentional processes. Interestingly, all these processes are deeply perturbed in patients with

schizophrenia,[17–19] further suggesting a disturbed long-ranged neural communication. As a coordinator of these large-network interactions, the beta frequency is therefore a prime candidate to be studied.

Although several EEG studies have been conducted on first episode psychosis (FEP) and chronic schizophrenia patients, studies on prodromal patients are scarce. This is unfortunate because schizophrenia is now increasingly seen as a neurodevelopmental disorder[20] and thus studying neurophysiological abnormalities in at-risk mental state (ARMS) patients would offer a unique opportunity to unravel the etiopathology of the disease.[19] Furthermore, previous studies on ARMS patients[21,22–24] did not make use of electrophysiological neuroimaging methods such as eLORETA which allows a reliable source localization of brain activity along with various connectivity analyses of frequencies.[25] Moreover, studies were frequently based on patients treated with antipsychotic drugs, which could have severely obfuscated the discovery of neurophysiological correlates of psychopathology.[26]

Thus, we compared beta and gamma oscillations in 3 relatively large and antipsychotic-naive groups, ie, ARMS patients with later transition to psychosis (ARMS-T), ARMS patients without later transition to psychosis (ARMS-NT) and healthy controls (HC). We not only assessed the current source density (CSD) at these frequency bands, but also their lagged phase synchronization across brain areas as a function of Euclidian distance. We hypothesized that ARMS-T patients would demonstrate abnormal CSD in both the high gamma and beta frequency bands when compared with ARMS-NT and HC. Furthermore, we postulated that the lagged phase synchronization of beta, the long-range modulator, would be more decreased in ARMS-T compared to ARMS-NT and HC as a function of increasing Euclidian distance.

## Methods

### Setting and Recruitment

The EEG data analyzed in this study were collected as part of the Basel *Früherkennung von Psy*chosen (*FePsy*) project, a prospective multilevel study, which aims to improve the early detection of psychosis.[27] The study was approved by the ethics committee of the University of Basel, and all participants provided written informed consent. Patients recruited for this study were help-seeking consecutive referrals to the *FePsy* Clinic at the University Psychiatric Clinics Basel, which was specifically set up to identify, assess, and treat individuals in the early stages of psychosis.

### Screening Procedure

We used the Basel Screening Instrument for Psychosis (BSIP)[28] to identify ARMS individuals. The BSIP is based on the PACE inclusion/exclusion criteria[29] and has been shown to have a high predictive validity and a good interrater reliability.[28] Exclusion criteria for patients were age younger than 18 years, insufficient knowledge of German, IQ < 70, previous episode of schizophrenic psychosis (treated with major tranquilizers for >3 weeks [lifetime] and 125 mg chlorpromazine equivalent/day), psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed depression or borderline personality disorder. For this study, we included all ARMS patients that were recruited for the *FePsy* study between March 2000 and August 2013 and had a clinical EEG session of at least 15 min at baseline assessment. They were followed-up at regular intervals in order to distinguish those who later transitioned to frank psychosis (ARMS-T) from those who did not (ARMS-NT). During the first year of the follow-up, ARMS individuals were assessed for transition to psychosis monthly, during the second and third years 3-monthly, and thereafter annually using the transition criteria of Yung et al.[29] In this study, individuals were only classified as ARMS-NT if they had a follow-up duration of at least 3 years and did not develop frank psychosis. HC were recruited from trade schools, hospital staff, and through advertisements. Inclusion criteria for the healthy participants were: no history of psychiatric or neurological disease, no past or present substance abuse or head trauma.

### EEG Recordings and Data Acquisition

EEG data were recorded at the University Hospital of Basel. Patients sat in a quiet room during eyes closed resting-state condition for about 20 min. Every 3 min, subjects were asked to open their eyes for a period of 5–6 s. At any signs of behavioral and/or EEG drowsiness, the patients were verbally asked to open their eyes. EEG data were sampled at a rate of 250 Hz by 19 gold cup electrodes (Nicolet Biomedical, Inc.) referenced to linked ears. Electrodes impedances were kept below 5Ω.

### Artifact Rejection

EEG pre-processing was performed using Brain Vision Analyzer 2.0 software (Brain Products GmbH). We processed each EEG in parallel split into 2 branches, one filtered at 0.5 Hz and one at 1 Hz. We did so in order to apply the ICA matrix from the most stable signal (1 Hz) to the one that conserved the most signal (0.5 Hz). Both branches were handled in the same way up to the step that involved re-referencing to the common average. As a first step, artifact rejection was performed manually, based on visual inspection, to remove epochs containing extreme ocular artifacts, muscles and/or cardiac contamination and bad signals due to random movements. Biased extended Infomax ICA analyses were then performed for the removal of residual eye movements, eye-blinking, muscles and non-biological

components contaminated with high gamma frequencies of 50 Hz and above as measured by Fast Fourier Transform (FFT) of the ICA components (resolution at 1 Hz, power $\mu V^2$, hanning window length of 10%). After applying the ICA corrected matrix of the data filtered at 1 Hz to the one filtered at 0.5 Hz, we re-referenced the data to common average. Finally, another manual rejection based on visual inspection was performed to exclude remaining artifacts as mentioned above.

### EEG Current Source Localization Density Analysis

To compute the cortical CSD of neural oscillations, we used exact low-resolution electromagnetic tomography (eLORETA)[25] on EEG data segmented into 2s epochs (on average 669 segments per subject). Patient groups did not significantly differ in number of segments. eLORETA is a neurophysiological imaging technique based on a weighted minimum norm inverse solution procedure allowing for the 3D modeling of the EEG CSD with an exact localization performance, but with a high correlation of neural sources that are in close proximity. Numerous studies based on neuroimaging tools, such as functional[30,31] and structural magnetic resonance imagery (MRI),[32] positron emission tomography (PET),[33–35] and intracranial EEG recordings,[36,37] have validated LORETA as an efficient and reliable tool to study brain activity. Compared with the first version of LORETA,[38] eLORETA has no localization bias in the presence of structured noise in simulated data.[39]

In eLORETA, a 3-shell spherical head model (brain, scalp, and skull compartments) is used and the solution space is restricted to the cortical gray matter/hippocampus, which comprises 6239 voxels of 5mm × 5mm × 5mm each. The head model for computing the lead field is based on the Montreal Neurological Institute (MNI) brain MRI average.[40]

### Lagged Phase Synchronization Analysis

For a spatially unbiased lagged phase synchronization analysis we defined regions of interests (ROIs) based on the MNI coordinates of the cortical voxel underlying the 19 electrode sites[41] (for technical details, see supplementary appendix 3). We used a single voxel for each ROI because eLORETA's spatial resolution is relatively low, and expanding the ROI to neighboring voxels could potentially bias the analysis due to the high correlation among them.[41] Next, we computed the lagged phase synchronization between all 19 ROIs resulting in a relatively high number (ie, 171) of pairwise combinations. Lagged phase synchronization quantifies the non-linear relationship between 2 ROIs after the instantaneous zero-lag contribution has been removed. Removing this instantaneous zero-lag contribution has been shown to eliminate non-physiological artifacts, such as volume conduction, which biases relationship measurements such as instantaneous

connectivity.[25] Finally, we used the statistical software R[42] for calculating the distances between ROIs in 3D in order to asses local vs global phase synchronization. The Euclidian distance between ROI1 ($x_1$, $y_1$, $z_1$) and ROI2 ($x_2$, $y_2$, $z_2$) were calculated using the Pythagorean theorem: $\sqrt{[(x_2-x_1)^2 + (y_2-y_1)^2 + (z_2-z_1)^2]}$ and were subsequently standardized into $z$-scores.

### Neurocognitive Assessment

In order to assess the participants' non-verbal capabilities to process and integrate higher-order relationships between individual entities we used the Leistungsprüfsystem Scale 3 (LPS-3), a well-established German intelligence scale for assessing nonverbal (abstract reasoning) abilities.[43] To assess working memory, we used the 2-back task of the Testbatterie zur Aufmerksamkeitsprüfung (TAP).[44]

### Assessment of Positive and Negative Psychotic Symptoms

The Brief Psychiatric Rating Scale Expanded (BPRS-E)[45,46] was used to assess positive and negative psychotic symptoms. The positive psychotic symptom scale was based on the 4 items hallucinations, suspiciousness, unusual thought content, and conceptual disorganization and the negative psychotic symptom scale was based on the items blunted affect, psychomotor retardation and emotional withdrawal, as defined by Velligan et al.[47]

### Statistical Analyses

In order to identify the CSD differences between groups (ARMS-NT vs HC, ARMS-T vs HC, ARMS-NT vs ARMS-T), we used statistical nonparametric mapping (SnPM).[48] The use of SnPM in eLORETA has been validated[49,50] and utilized in previous clinical studies.[41,51] Differences in cortical oscillations between groups in each frequency band were assessed by voxel-by-voxel independent sample $F$-ratio-tests with a frequency wise normalization. To correct for multiple comparisons across all voxels and all frequencies, a total of 5000 permutations were used to calculate the critical probability threshold (5% probability level).

Next, CSD values were extracted at those ROI that differed between groups and their association with LPS-3 and 2-back tasks performance scores was assessed by linear regression models using neuropsychological performance scores as dependent variables and CSD values, diagnostic group, age, and years of education as independent variables. To test whether the associations between CSD values and neuropsychological performance differed between groups, an interaction term between group and CSD values was included. In addition to this ROI approach, a whole brain analysis was performed by correlating voxel-wise these performance measures with CSD. Furthermore, to correct for multiple testing, this whole brain analysis was based on 5000 permutations to

determine the empirical probability distribution for the maximal statistics under the null hypothesis.[41,52]

To assess group differences in lagged phase synchronization, we fitted a linear mixed-effects model using lagged phase synchronization of the ROI pairs (171 pairs) as the dependent variable and Euclidian distance (within-subjects) and group (between-subjects) along with their interaction as independent variables. The model also included an intercept term that randomly varied per individual. To investigate the impact of positive and negative symptoms on the lagged phase synchronization as a function of anatomical distances, we applied linear mixed-effects models that additionally included BPRS positive and negative symptoms as independent variables. Furthermore, these analyses were repeated for each of the seven different frequencies and corrected for multiple comparison using the Benjamini–Hochberg method.[53]

## Results

### Sample Description

Until August 2013, 134 ARMS patients and 97 HC were recruited for the **FePsy** study. Of these, 63 ARMS and 29 HC had sufficient EEG and follow-up data to be included in the present study. Twenty-three of the included ARMS patients had made a transition to psychosis (ARMS-T) during the follow up and 40 had not (ARMS-NT). None of those who made a transition converted to psychotic mood disorder. The 71 ARMS individuals that were excluded from this study did not differ from the included ARMS individuals with regard to gender, sex, years of education, and BPRS total and positive symptoms scores. Demographic and clinical characteristics of the 3 groups (ie, HC, ARMS-T, and ARMS-NT) are shown in table 1. There was a small overall difference in age ($P = .046$), which was due to a lower age in HC compared to ARMS-NT, significant at a trend level ($P = .053$). Furthermore, ARMS-T patients had higher positive symptoms than ARMS-NT ($P = .005$). Almost all ARMS individuals were antipsychotic naïve; only 4 ARMS individuals (4/63) had received low doses of second-generation antipsychotic medication during no more than 3 weeks for behavioral control by the referring psychiatrist or general practitioner prior to study inclusion.

**Table 1.** Demographic and Clinical Characteristics of HC, ARMS-T, and ARMS-NT Individuals

| | HC N = 29 | ARMS-NT N = 40 | ARMS-T N = 23 | P Value |
|---|---|---|---|---|
| Gender | | | | .597 |
| Women | 14 (48.3%) | 15 (37.5%) | 11 (47.8%) | |
| Men | 15 (51.7%) | 25 (62.5%) | 12 (52.2%) | |
| Age | 22.4 (5.02) | 26.5 (8.42) | 26.3 (7.13) | .046 |
| Years of education | 11.9 (1.93) | 11.6 (3.49) | 11.2 (2.41) | .693 |
| Antidepressants currently | | | | 1.000 |
| No | | 30 (75.0%) | 17 (73.9%) | |
| Yes | | 10 (25.0%) | 6 (26.1%) | |
| Antipsychotics currently | | | | .619 |
| No | | 38 (95.0%) | 21 (91.3%) | |
| Yes | | 2 (5.00%) | 2 (8.70%) | |
| Mood stabilizer currently | | | | .365 |
| No | | 40 (100%) | 22 (95.7%) | |
| Yes | | 0 (0.00%) | 1 (4.35%) | |
| Tranquilizer currently | | | | .713 |
| No | | 35 (87.5%) | 19 (82.6%) | |
| Yes | | 5 (12.5%) | 4 (17.4%) | |
| BPRS positive symptoms | | 6.33 (2.39) | 8.67 (2.71) | .001 |
| BPRS negative symptoms | | 5.60 (2.72) | 5.40 (2.74) | .795 |
| BPRS total score | | 37.7 (10.5) | 42.1 (9.89) | .137 |
| Risk group | | | | .116 |
| Prepsychotic only (APS or BLIPS) | | 25 (62.5%) | 18 (78.3%) | |
| Genetic risk only | | 3 (7.50%) | 0 (0.00%) | |
| Mixed prepsychotic + genetic | | 6 (15.0%) | 5 (21.7%) | |
| Unspecific only | | 6 (15.0%) | 0 (0.00%) | |
| LPS (nonverbal IQ) | 119 (9.31) | 115 (10.6) | 112 (14.3) | .204 |
| 2-back task correct responses | 13.5 (1.46) | 12.0 (3.24) | 11.2 (2.51) | .044 |
| Days between EEG and transition to psychosis | | | 423 (449) | |

*Note:* HC, healthy controls; ARMS-NT, at-risk mental state patients without later transition to psychosis; ARMS-T, at-risk mental state patients with later transition to psychosis; BPRS, Brief Psychiatric Rating Scale; LPS, Leistungsprüfsystem; APS, attenuated psychotic symptoms; BLIPS, brief, limited intermittent psychotic symptoms. Categorical and continuous variables were compared by Pearson $\chi^2$ (or Fisher's exact tests if any expected cell frequencies were <5) and ANOVAs, respectively.
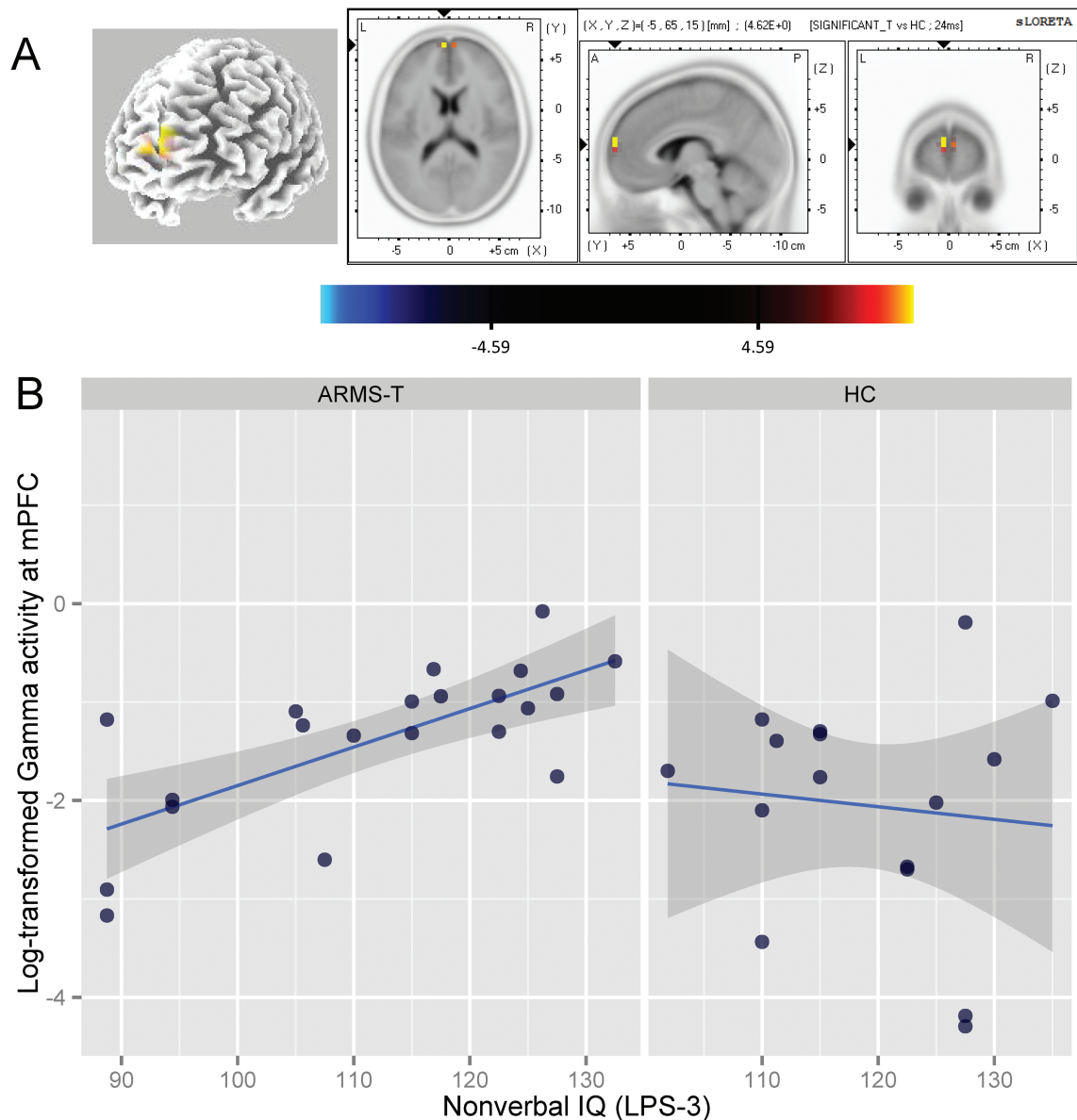
*Source Localization*

The average CSD in ARMS-T, ARMS-NT, and HC at each frequency band are depicted in figure 1. In ARMS-T and ARMS-NT, the highest CSD values were present in the delta (0.82 vs 0.63 $\mu$A/mm$^2$) followed by the gamma frequency band (0.67 vs 0.57 $\mu$A/mm$^2$), whereas in HC they were in alpha2 (0.55 $\mu$A/mm$^2$) and delta (0.43 $\mu$A/mm$^2$), respectively. In ARMS-T patients delta activity seemed to be relatively distributed throughout the cortex, particularly in frontal and parieto-occipital areas, while in HC and ARMS-NT delta activity was more localized in the frontal cortex. In the gamma band, source frontal activity seemed to progressively increase from HC to ARMS-NT to ARMS-T. Interestingly, statistical analyses confirmed that ARMS-T had increased gamma activity in the medial prefrontal cortex (mPFC) bilaterally (BA 10), with a global maximum in the left hemisphere ($X = -5$, $Y = 66$, $Z = 15$, $t = 4.59$, $P < .05$, corrected) (see figure 2a).

*Current Source Analyses and Neurocognitive Measurements*

A linear regression model with cognitive performance in the LPS-3 as dependent variables and CSD activity in the gamma frequency band at the mPFC and group (ARMS-T vs HC) as independent variables revealed a significant main effect of group ($P < .001$, corrected) and interaction between group and mPFC activity ($P < .001$, corrected). This interaction was due to a positive relationship between LPS-3 and mPFC activity in the ARMS-T group ($P < .001$, corrected) but not in HC ($P = .140$, corrected) (see figure 2b). In a similar model including performance in the 2-back task as dependent variable, there were no significant main effect of mPFC activity and interaction effect between mPFC activity and group when corrected for multiple comparisons. These results were also found using conventional EEG measurements (supplementary appendix 1). A whole brain voxel-wise correlation analysis revealed that the CSD of gamma oscillations was highly correlated with LPS-3 performance in ARMS-T ($r = .734$, $P < .001$, corrected), but not in ARMS-NT and HC, and the global maximum was located at ($X = -5$, $Y = 65$, $Z = 15$) (supplementary appendix 2).

*Lagged Phase Synchronization Across Distributed Brain Regions*

Linear mixed-effects models with lagged phase synchronization as dependent variables, Euclidian distance, group and their interaction as independent variable and a random intercept per subject, revealed significant main effects of Euclidian distance for each frequency band (all $P$s $< .001$, corrected). This was due to decreased lagged phase synchronization with increasing distances between the ROIs (171 pairs) in all frequencies except for the delta band, which demonstrated an opposite association. In addition, there was a significant interaction between group and Euclidian distance for lagged phase synchronization



**Fig. 1.** For illustrative purposes, the average current source density ($\mu$A/mm$^2$) by group and frequency bands.

**Fig. 2.** (A) eLORETA statistical map of gamma band differences between ARMS-T and HC and (B) correlations between gamma activity (μA/mm$^2$) at the medial prefrontal cortex (mPFC) and LPS-3 performance in ARMS-T and HC.

of beta1 oscillations ($P < .001$, corrected), which was due to a stronger decrease of lagged phase synchronization with increasing anatomical distance in the ARMS-T group compared to the ARMS-NT and HC groups (see figure 3).

Moreover, a linear mixed-effect model that additionally included BPRS positive symptoms as an independent variable revealed a significant second order interaction between lagged phase synchronization, distance and BPRS positive symptoms in the beta1 frequency band ($P = .002$, corrected), indicating that higher positive symptoms in the ARMS-T group was associated with a particular strong decrease of lagged phase synchronization with increasing distance (see figure 4a). The same interaction occurred with negative symptoms ($P = .022$,

corrected) (see figure 4b). In both models, the interaction between Euclidian distance and group remained significant, indicating that this interaction was not due to different psychopathology in ARMS-T and ARMS-NT.

**Discussion**

In this study, we assessed by means of electrophysiological neuroimaging methods the CSD distribution and lagged-phase synchronization of neural oscillations across brain areas in patients at-risk for psychosis and HC. Consistent with our predictions, we found: (1) in comparison to HC, increased CSD of frontal gamma oscillations (30–50 Hz) in those patients who later transitioned to psychosis. Moreover, in ARMS-T gamma activity was positively
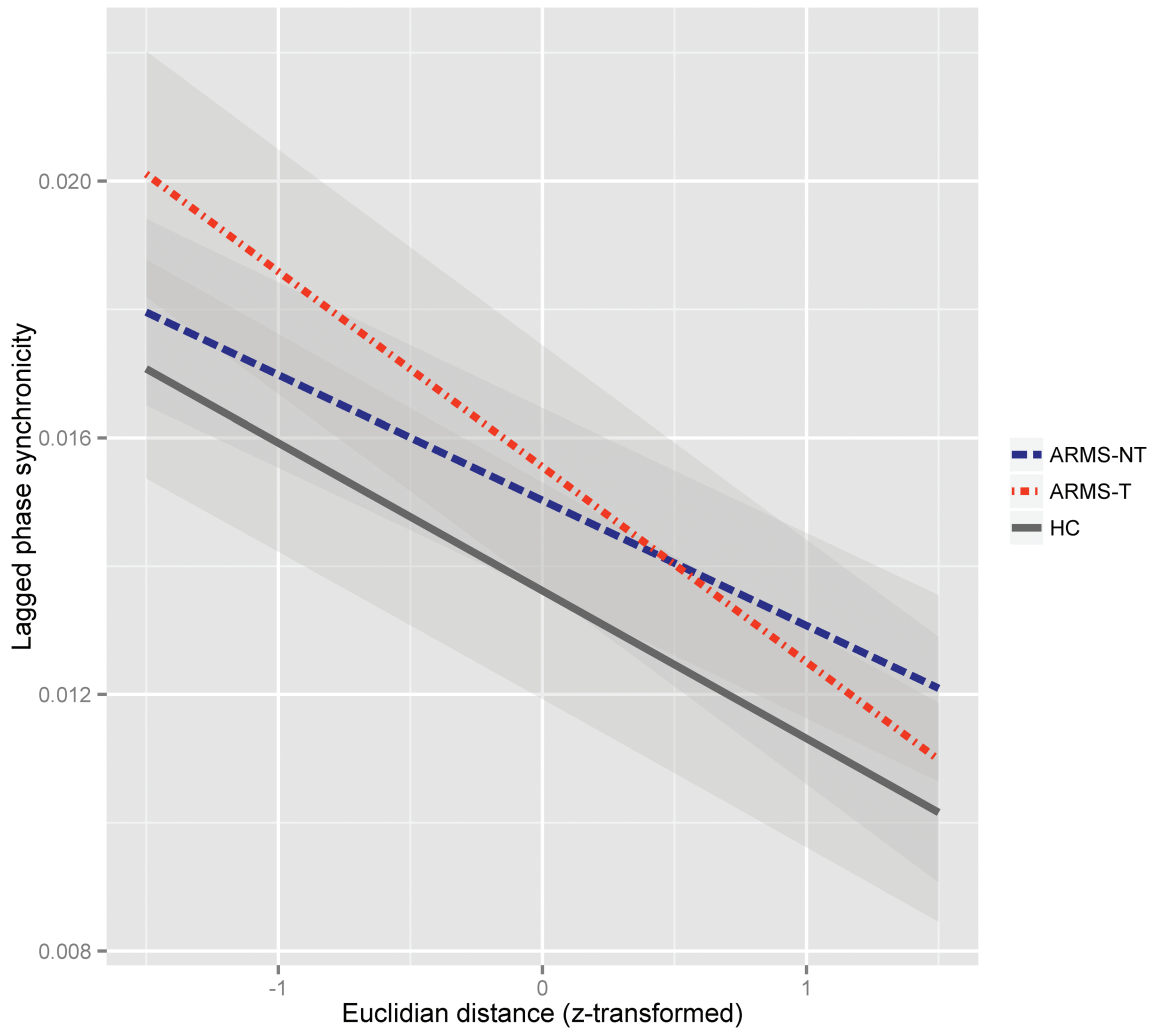
**Fig. 3.** The lagged phase-synchronization of the beta 1 frequency band as a function of distance. Shaded areas cover regression coefficients with ±1 SE.

correlated with cognitive performance as assessed by the LPS-3. (2) We revealed that the inverse relationship between lagged phase synchronization and Euclidian distance was steeper in the ARMS-T patients than the other groups. This effect was most pronounced in patients with elevated negative and positive symptoms. These findings provide strong evidence that patients who will later make the transition to psychosis are characterized by impairments in neural oscillations.

*CSD Analyses*

The revealed alteration in mPFC gamma oscillations in ARMS-T patients is in line with numerous studies reporting abnormal gamma oscillations in schizophrenia[2,54,55] and extends these findings by demonstrating that prefrontal gamma oscillations are already affected in high-risk patients that later transitioned to psychosis. Although both an increase and a decrease of gamma oscillations have extensively been documented in patients suffering

from psychosis, an increase has mostly been found in unmedicated patients exhibiting positive symptoms.[11] This is in line with our ARMS-T patients who fit these criteria and could explain the here revealed increase in the medial prefrontal gamma oscillations.

As the mPFC has been shown to be modulated by gamma oscillations[56] and to be associated with seemingly disparate cognitive functions such as detecting high-order relationships,[57–60] planning and visualizing the future[61] and constructing social and emotional judgments,[62] our finding of increased gamma activity suggests that ARMS-T patients, already at baseline, have an impaired mPFC that could potentially explain cognitive abnormalities.[63,64] Indeed, we found that gamma oscillation in mPFC [Brodmann area (BA) 10] correlated with neurocognitive performance in the LPS-3, a task in which patients are asked to find which item does not belong to a series of shapes. Such a detection of a higher-order relationship between individual entities was previously found to be associated with activation in BA 10 in semantic[57,59]
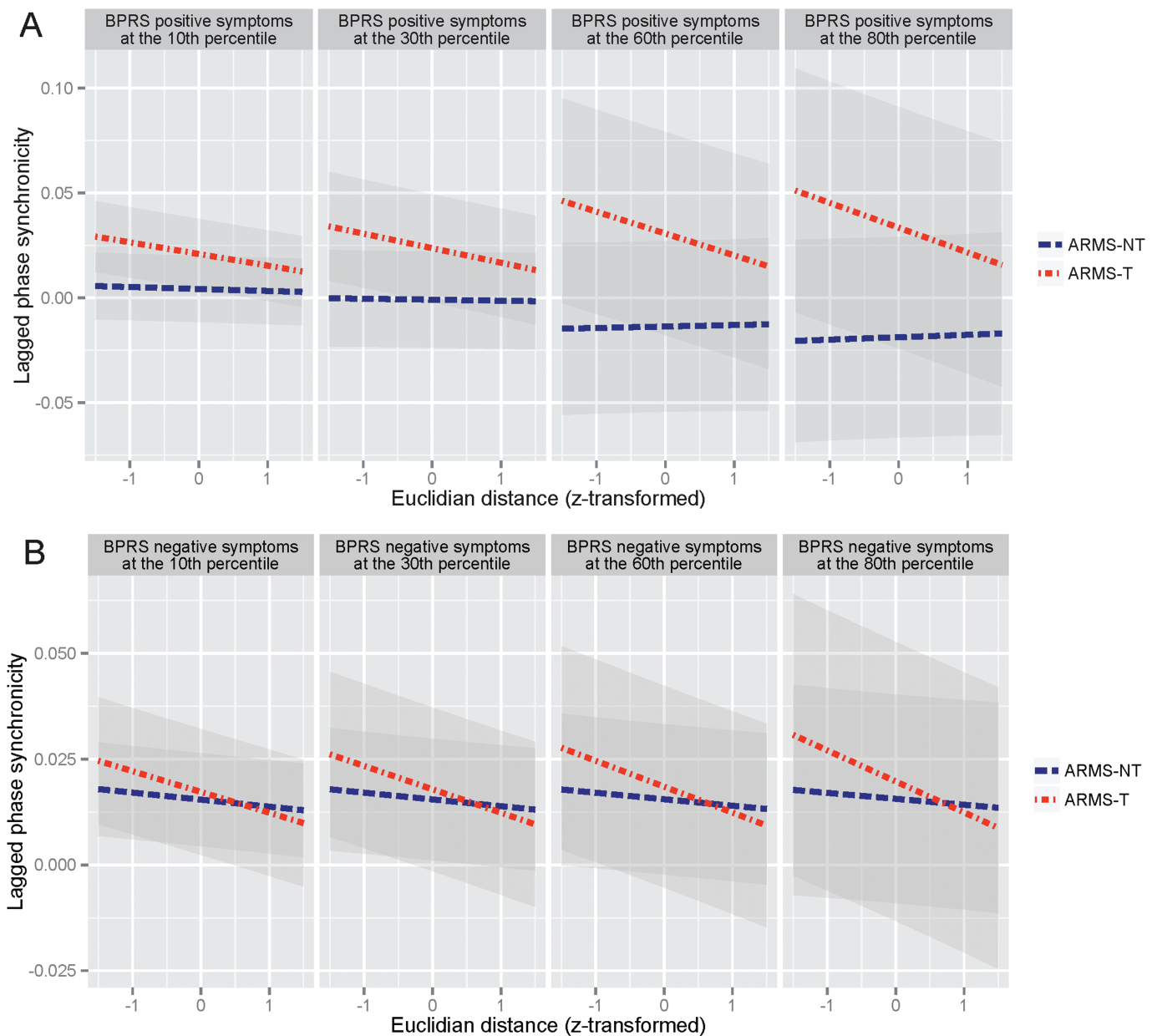
**Fig. 4.** (A) The lagged phase-synchronization of the beta 1 frequency band as a function of distance for each of 4 different values of BPRS positive symptoms. (B) The lagged phase-synchronization of the beta 1 frequency band as a function of distance for each of 4 different values of BPRS negative symptoms. Shaded areas cover regression coefficients with ±1 SE.

and visual-based tasks,[58,60] which is in line with the here revealed association between LPS-3 performance and mPFC gamma oscillations. However, the correlation between LPS-3 performance and gamma oscillations was positive, suggesting that increased medial prefrontal gamma oscillations in the ARMS-T group may be an adaptive and compensatory process. A speculative explanation would be that patients with a high capacity to detect higher-order relationships, as indexed by the LPS-3 test and by gamma oscillation in the BA10, are more cognitively equipped to make sense of their altered psychological state.

*Lagged Phase Synchronization Across Distributed Brain Regions*

We revealed that ARMS-T patients show stronger decreasing lagged phase synchronicity with increasing Euclidian distance than ARMS-NT and HC (figure 3). This negative association is particularly present in patients with high positive symptoms (figure 4).

Thus, through the increased synchronization in the shorter inter-regional distances of the brain characterized in ARMS-T individuals, the influence of the long-range synchronicity is reduced. This could result from the disruption in the volume and organization of anatomical

connections, which is supported by the findings of reduced grey matter volume in ARMS-T[65] and its association with beta oscillations.[3] Therefore, this could lead to the situation that distributed cortical areas can no longer communicate efficiently and that psychological entities like perception and cognition are no longer adequately integrated. These findings support the increasingly accepted notion that the neuropsychological impairments associated with schizophrenic psychoses are due to distributed impairments involving the coordinated activity among numerous cortical areas.[3] Importantly, given that we observed increased synchronization in the beta1 band already before transition to psychosis, this could indicate an increased liability for psychosis and thereby help to improve the prediction of psychosis.

*Limitations*

The results of the present study are constrained by a number of limitations: All data were acquired using a relatively low-density EEG system which is commonly used in the clinical field for practical reasons. Even though numerous recent studies have shown that CSD and connectivity analyses during resting-state could reliably be performed using a 19 channels EEG system,[66–68] we believe that the true potential of the eLORETA analyses could not be fully utilized. Moreover, to control for the strong correlation between adjacent voxels in the phase synchronization analyses, we could only choose 19 ROIs that would be measured by 19 channels and yield only 171 connections. Therefore, future studies should conduct these analyses again using higher density EEG systems.

## Conclusion

Taken together, our result of a heightened gamma activity in the mPFC in ARMS-T patients could potentially reveal the neural underpinnings for an abnormal cognitive integration. Moreover, the increased lagged phase synchronicity characterized across smaller inter-regional brain areas in the beta1 frequency suggests anatomical abnormalities that could be hindering the proper communication between various cortical areas. These findings provide strong evidence that patients who will later make the transition to psychosis are characterized by impairments in neural oscillations.

## Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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## References

1. Kindler J, Hubl D, Strik WK, Dierks T, Koenig T. Resting-state EEG in schizophrenia: auditory verbal hallucinations are related to shortening of specific microstates. *Clin Neurophysiol*. 2011;122:1179–1182.

2. Light GA, Hsu JL, Hsieh MH, et al. Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biol Psychiatry*. 2006;60:1231–1240.

3. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci*. 2010;11:100–113.

4. Phillips WA, Silverstein SM. Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behav Brain Sci*. 2003;26:65–82; discussion 82.

5. Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. *Science*. 2004;304:1926–1929.

6. Farzan F, Barr MS, Levinson AJ, et al. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain*. 2010;133:1505–1514.

7. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci*. 2012;35:57–67.

8. Minzenberg MJ, Firl AJ, Yoon JH, Gomes GC, Reinking C, Carter CS. Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. *Neuropsychopharmacology*. 2010;35:2590–2599.

9. Jensen O, Kaiser J, Lachaux JP. Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci*. 2007;30:317–324.

10. Gallinat J, Winterer G, Herrmann CS, Senkowski D. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin Neurophysiol*. 2004;115:1863–1874.

11. Lee KH, Williams LM, Breakspear M, Gordon E. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. *Brain Res Brain Res Rev*. 2003;41:57–78.

12. Herrmann CS, Demiralp T. Human EEG gamma oscillations in neuropsychiatric disorders. *Clin Neurophysiol*. 2005;116:2719–2733.

13. Kopell N, Ermentrout GB, Whittington MA, Traub RD. Gamma rhythms and beta rhythms have different synchronization properties. *Proc Natl Acad Sci U S A*. 2000;97:1867–1872.

14. Bibbig A, Traub RD, Whittington MA. Long-range synchronization of gamma and beta oscillations and the plasticity of excitatory and inhibitory synapses: a network model. *J Neurophysiol*. 2002;88:1634–1654.

15. Tallon-Baudry C, Bertrand O, Fischer C. Oscillatory synchrony between human extrastriate areas during visual short-term memory maintenance. *J Neurosci*. 2001;21:RC177.

16. von Stein A, Rappelsberger P, Sarnthein J, Petsche H. Synchronization between temporal and parietal cortex during multimodal object processing in man. *Cereb Cortex*. 1999;9:137–150.

17. Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry*. 2013;70:1107–1112.

18. Keefe RS, Harvey PD. Cognitive impairment in schizophrenia. *Handb Exp Pharmacol*. 2012;213:11–37.

19. Riecher-Rössler A, Pflueger MO, Aston J, et al. Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. *Biol Psychiatry*. 2009;66:1023–1030.

20. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468:187–193.

21. Zimmermann R, Gschwandtner U, Wilhelm FH, Pflueger MO, Riecher-Rössler A, Fuhr P. EEG spectral power and negative symptoms in at-risk individuals predict transition to psychosis. *Schizophr Res*. 2010;123:208–216.

22. Gschwandtner U, Pflueger MO, Semenin V, Gaggiotti M, Riecher-Rössler A, Fuhr P. EEG: a helpful tool in the prediction of psychosis. *Eur Arch Psychiatry Clin Neurosci*. 2009;259:257–262.

23. van Tricht MJ, Ruhrmann S, Arns M, et al. Can quantitative EEG measures predict clinical outcome in subjects at clinical high risk for psychosis? A prospective multicenter study. *Schizophr Res*. 2014;153:42–47.

24. Ranlund S, Nottage J, Shaikh M, et al. Resting EEG in psychosis and at-risk populations—a possible endophenotype? *Schizophr Res*. 2014;153:96–102.

25. Pascual-Marqui RD, Lehmann D, Koukkou M, et al. Assessing interactions in the brain with exact low-resolution electromagnetic tomography. *Philos Trans A Math Phys Eng Sci*. 2011;369:3768–3784.

26. Jones NC, Reddy M, Anderson P, Salzberg MR, O'Brien TJ, Pinault D. Acute administration of typical and atypical antipsychotics reduces EEG γ power, but only the preclinical compound LY379268 reduces the ketamine-induced rise in γ power. *Int J Neuropsychopharmacol*. 2012;15:657–668.

27. Riecher-Rössler A, Gschwandtner U, Aston J, et al. The Basel early-detection-of-psychosis (FEPSY)-study—design and preliminary results. *Acta Psychiatr Scand*. 2007;115(2):114–125.

28. Riecher-Rössler A, Aston J, Ventura J, et al. The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity. *Fortschr Neurol Psychiatr*. 2008;76:207–216.

29. Yung AR, Phillips LJ, McGorry PD, et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl*. 1998;172:14–20.

30. Vitacco D, Brandeis D, Pascual-Marqui R, Martin E. Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. *Hum Brain Mapp*. 2002;17:4–12.

31. Mulert C, Jäger L, Schmitt R, et al. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. *Neuroimage*. 2004;22:83–94.

32. Worrell GA, Lagerlund TD, Sharbrough FW, et al. Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. *Brain Topogr*. 2000;12:273–282.

33. Zumsteg D, Wennberg RA, Treyer V, Buck A, Wieser HG. H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. *Neurology*. 2005;65:1657–1660.

34. Pizzagalli D, Oakes T, Fox A, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Mol Psychiatry* 2003;9:393–405.

35. Dierks T, Jelic V, Pascual-Marqui RD, et al. Spatial pattern of cerebral glucose metabolism (PET) correlates with localization of intracerebral EEG-generators in Alzheimer's disease. *Clin Neurophysiol*. 2000;111:1817–1824.

36. Zumsteg D, Friedman A, Wieser HG, Wennberg RA. Propagation of interictal discharges in temporal lobe epilepsy: correlation of spatiotemporal mapping with intracranial foramen ovale electrode recordings. *Clin Neurophysiol*. 2006;117:2615–2626.

37. Zumsteg D, Lozano AM, Wennberg RA. Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. *Clin Neurophysiol*. 2006;117:1602–1609.

38. Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int J Psychophysiol*. 1994;18:49–65.

39. Pascual-Marqui RD. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. *arXiv preprint*. 2007;*arXiv:07103341*.

40. Mazziotta J, Toga A, Evans A, et al. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos Trans R Soc Lond B Biol Sci*. 2001;356:1293–1322.

41. Canuet L, Tellado I, Couceiro V, et al. Resting-state network disruption and APOE genotype in Alzheimer's disease: a lagged functional connectivity study. *PLoS ONE*. 2012;7:e46289.

42. R Core Team. *R: A Language and Environment for Statistical Computing [computer program]. Version 3.0.2*; 2013.

43. Horn W. *LPS Leistungsprüfsystem*. Göttingen: Hogrefe; 1983.

44. Kirchner WK. Age differences in short-term retention of rapidly changing information. *J Exp Psychol*. 1958;55:352–358.

45. Ventura J, Green MF, Shaner A, Liberman RP. Training and quality assurance with the Brief Psychiatric Rating Scale: "the drift busters." *Int J Methods Psychiatr Res*. 1993;3:221–244.

46. Lukoff D, Nuechterlein K, Ventura J. Manual for the expanded brief psychiatric rating scale. *Schizophr Bull*. 1986;12:594–602.

47. Velligan D, Prihoda T, Dennehy E, et al. Brief psychiatric rating scale expanded version: how do new items affect factor structure? *Psychiatry Res*. 2005;135:217–228.

48. Holmes AP, Blair RC, Watson JD, Ford I. Nonparametric analysis of statistic images from functional mapping experiments. *J Cereb Blood Flow Metab*. 1996;16:7–22.

49. Anderer P, Pascual-Marqui RD, Semlitsch HV, Saletu B. Differential effects of normal aging on sources of standard N1, target N1 and target P300 auditory event-related brain potentials revealed by low resolution electromagnetic tomography (LORETA). *Electroencephalogr Clin Neurophysiol*. 1998;108:160–174.

50. Pascual-Marqui RD, Lehmann D, Koenig T, et al. Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. *Psychiatry Res*. 1999;90:169–179.

51. Canuet L, Ishii R, Iwase M, et al. Psychopathology and working memory-induced activation of the prefrontal cortex in schizophrenia-like psychosis of epilepsy: Evidence from magnetoencephalography. *Psychiatry Clin Neurosci*. 2011;65:183–190.

52. Hubl D, Koenig T, Strik WK, Garcia LM, Dierks T. Competition for neuronal resources: how hallucinations make themselves heard. *Br J Psychiatry*. 2007;190:57–62.

53. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B Methodol*. 1995;57:289–300.

54. Ferrarelli F, Massimini M, Peterson MJ, et al. Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. *Am J Psychiatry*. 2008;165:996–1005.

55. Pomarol-Clotet E, Salvador R, Sarró S, et al. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychol Med*. 2008;38:1185–1193.

56. Minzenberg MJ, Firl AJ, Yoon JH, Gomes GC, Reinking C, Carter CS. Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. *Neuropsychopharmacology*. 2010;35:2590–2599.

57. Wendelken C, Nakhabenko D, Donohue SE, Carter CS, Bunge SA. "Brain is to thought as stomach is to ??": investigating the role of rostrolateral prefrontal cortex in relational reasoning. *J Cogn Neurosci*. 2008;20:682–693.

58. Bunge SA, Helskog EH, Wendelken C. Left, but not right, rostrolateral prefrontal cortex meets a stringent test of the relational integration hypothesis. *Neuroimage*. 2009;46:338–342.

59. Bunge SA, Wendelken C, Badre D, Wagner AD. Analogical reasoning and prefrontal cortex: evidence for separable retrieval and integration mechanisms. *Cereb Cortex*. 2005;15:239–249.

60. Smith R, Keramatian K, Christoff K. Localizing the rostrolateral prefrontal cortex at the individual level. *Neuroimage*. 2007;36:1387–1396.

61. Barbey AK, Krueger F, Grafman J. Structured event complexes in the medial prefrontal cortex support counterfactual representations for future planning. *Philos Trans R Soc Lond B Biol Sci*. 2009;364:1291–1300.

62. Mitchell JP, Banaji MR, Macrae CN. The link between social cognition and self-referential thought in the medial prefrontal cortex. *J Cogn Neurosci*. 2005;17:1306–1315.

63. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol*. 2012;8:49–76.

64. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev*. 2009;33:279–296.

65. Borgwardt SJ, McGuire PK, Aston J, et al. Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. *Br J Psychiatry Suppl*. 2007;51:s69–s75.

66. Babiloni C, Bosco P, Ghidoni R, et al. Homocysteine and electroencephalographic rhythms in Alzheimer disease: a multicentric study. *Neuroscience*. 2007;145:942–954.

67. Gianotti LR, Künig G, Lehmann D, et al. Correlation between disease severity and brain electric LORETA tomography in Alzheimer's disease. *Clin Neurophysiol*. 2007;118:186–196.

68. Babiloni C, Carducci F, Lizio R, et al. Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease. *Hum Brain Mapp*. 2013;34:1427–1446.