First publ. in: Biological Psychiatry 68 (2010), 7, pp. 595-598
doi:10.1016/j.biopsych.2010.06.013

Alpha Phase Locking Predicts Residual Working Memory Performance in Schizophrenia

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Background: Working memory (WM) deficits are a core feature of schizophrenia. Recent electrophysiological evidence indicates that the brain systems for visual encoding are especially impaired. However, patients still achieve performance levels clearly above chance, which indicates the existence of residual mechanisms supporting WM encoding. The present study presents evidence that alpha phase locking of the electroencephalogram is a marker for such residual cognitive mechanisms.

Methods: Alpha phase locking during encoding into WM was compared between 17 patients with early-onset schizophrenia (EOS) and 17 healthy control subjects. Results of phase locking were correlated with accuracy. A median split based on alpha phase locking in patients was used to compare accuracy between control subjects and patients with high and low alpha phase locking.

Results: Alpha phase locking increased with WM memory load in both EOS and control subjects, although alpha phase locking was generally reduced in EOS. Furthermore, for EOS, a positive correlation between alpha phase locking and performance was obtained. Additionally, patients exhibiting high phase locking did not differ in performance from control subjects.

Conclusions: These results provide the first evidence for a relationship between alpha phase locking and visual WM encoding. This neural mechanism seems to be preserved in some patients with schizophrenia and then allows them to attain normal performance levels.

Key Words: Alpha phase locking, EEG, schizophrenia, working memory

Deficits in working memory (WM) are a cardinal feature of schizophrenia, underlying cognitive impairment in other domains and predicting social and occupational dysfunction. It is increasingly recognized that deficits in encoding make an important contribution to the WM impairments of patients with schizophrenia (1).

Recent models of cognitive deficits have emphasized the potential role of neural synchrony as a pathophysiological mechanism underlying impaired WM performance, suggesting that impaired encoding of information may be related to deficits in sustaining precisely timed synchronized activity patterns.

In previous studies, we showed that the event-related potential component P1, as well as early evoked oscillatory activity (4–30 Hz), predicted successful WM encoding in control subjects but not in adolescent patients with schizophrenia (2,3). Patients showed reduced activity in both the P1 and the evoked oscillatory activity. The finding of a reduced P1 component in schizophrenic patients complements other findings, which showed that these patients demonstrate a general reduction in alpha oscillatory activity (4). Several lines of research indicate that alpha (~10 Hz) phase locking contributes to the generation of the P1 component (5,6). Phase locking describes the variability of the phase of a neural signal (commonly oscillations in a particular frequency band) across single trials in relation to an external event (Supplementary Methods in Supplement 1). Previous studies demonstrated that patients show a reduction in phase locking, which suggests an increase in neuronal response variability ("cortical noise" [7]). For instance, there is evidence that the sensory gating deficit in patients with schizophrenia may, in part, be explained by reduced alpha phase locking (8). Furthermore, a negative relationship between frontal background noise (indicating a lack of phase resetting) across a range of frequency bands including alpha in an auditory oddball task and the N-back working memory task has been reported (7). Whether there is also a direct relationship between alpha phase locking and deficits in working memory encoding, however, is unclear to date.

Despite the reductions in the evoked oscillatory activity and the reduced P1 component, which are crucial for working memory encoding, patients still achieved an accuracy level clearly above chance (> 80%). These behavioral data strongly suggest the existence of at least a residually functioning mechanism that enables the patients to perform the task. However, electrophysiological correlates of such residual mechanisms have not been described. Here, we show that alpha phase locking during encoding indexes working memory performance and is preserved in the high-performing patients.

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Methods and Materials

Seventeen patients with early-onset schizophrenia diagnosed according to DSM-IV criteria were compared with 17 control participants matched for age, gender, handedness, and premorbid IQ; for participants' details, see Haenschel *et al.* (2). All patients were on medication at the time of testing with a mean chlorpromazine equivalent medication of 188.7 mg/day (SD = 166). The study was approved by the ethics committee of the Medical School, Goethe University, Frankfurt am Main, Germany.

A delayed discrimination task was implemented using the Experimental-Run-Time-System (ERTS) software (www.erts.de) (Figure S1 in Supplement 1). It probes load effects in visual WM with 36 novel visual objects that were presented in the center of the computer monitor (visual angle, 1.34°) Trials with different WM load levels were randomly distributed across sessions with a total of 50 trials obtained per WM load level. Event-related potential and time

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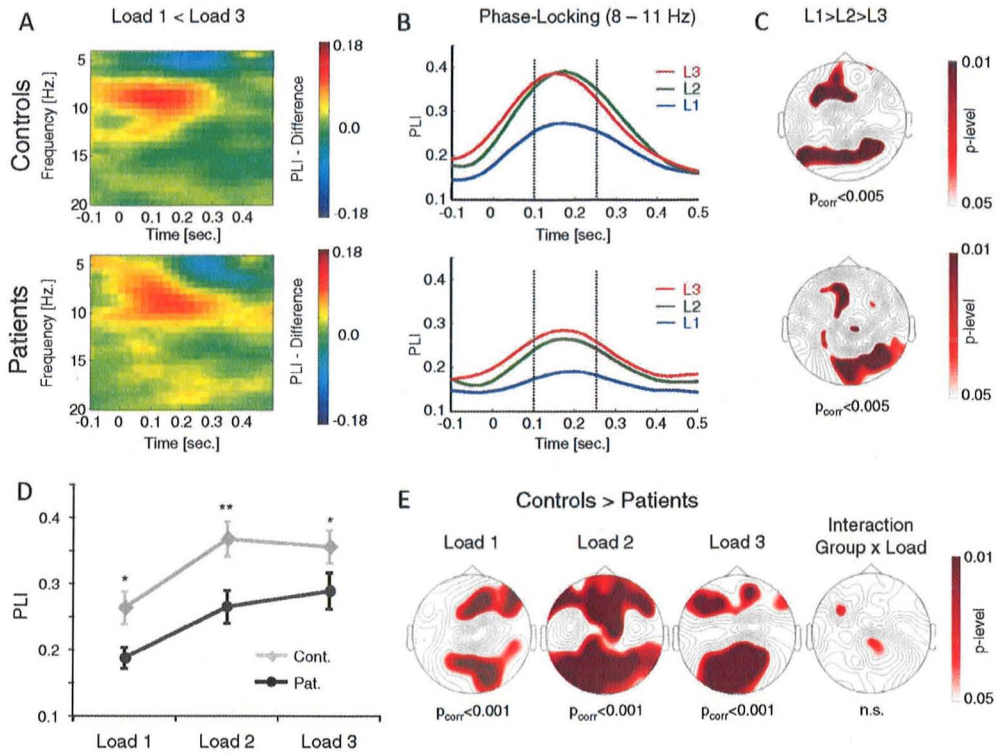

Figure 1. The results of alpha phase locking are plotted. **(A)** A time-frequency plot showing the difference in Phase-Locking Index (PLI) between load 1 and load 3 is shown for control subjects (upper panel) and patients (lower panel). Red colors indicate stronger PLI in load 3 compared with load 1. **(B)** The time course of alpha PLI is shown for the three working memory (WM) load conditions. The dotted lines indicate the time window that was used for statistical analysis and the topographical plots. For the plots in **(A)** and **(B)**, the PLI was averaged across those electrode sites, exhibiting a significant effect of WM load. **(C)** The topography of the WM load effects are plotted by means of p levels, obtained by nonparametric Friedman analyses of variance. Red colors indicate p levels $< .05$. P_{corr} refers to the p level obtained by the randomization procedure (Supplementary Methods in Supplement 1). **(D)** The mean alpha PLI, averaged across the significant electrode sites **(C)**, for the three WM load conditions is shown for control subjects (gray) and patients (black). Control subjects show higher levels of alpha PLI in each of the three WM load conditions ($^*p < .05$; $^{**}p < .01$; nonparametric Mann-Whitney tests). Error bars indicate mean SE. **(E)** The topographies indicate significant differences between control subjects and patients for each WM load condition (nonparametric Mann-Whitney tests). P_{corr} refers to the p level obtained by the randomization procedure. The group by load interaction plot on the right shows that the increase in alpha PLI, from load 1 to load 3, was comparable for both patients and control subjects. L, load; n.s., nonsignificant.

frequency (but not phase locking) analyses have been reported previously (2,3).

Recording, digitization, and preprocessing of the 64-channel electroencephalogram data were carried out with a BrainAmp amplifier and the BrainVision Recorder software (Brain Products, Gilching, Germany). The electroencephalogram was recorded at a sampling rate of 500 Hz. Electrode impedance was kept below 5 kΩ. Only trials with correct responses were included. We analyzed the final sample stimulus in each WM load condition, i.e., the first stimulus for a load of 1, the second stimulus for a load of 2, and the third for a load of 3 (Figure S1 in Supplement 1). Phase locking was calculated by means of the Phase-Locking Index (9). For a detailed description of the phase-locking analysis and the statistical procedure, see Supplementary Methods and Figure S2 in Supplement 1. In addition to alpha phase locking, we also analyzed induced alpha power (Figure S3 in Supplement 1).

Results

Behavioral Results

As reported in Haenschel *et al.* (2), patients exhibited reduced performance levels in the WM task compared with control subjects [group: $F(1,32) = 24.98, p < .001$]. Both groups showed a significant WM load effect, indicating that accuracy dropped with increasing WM load.

Alpha Phase Locking

The results of the alpha phase-locking analysis are summarized in Figure 1. As shown in Figure 1A, a pronounced effect of WM load on alpha phase locking was observed around 100 to 250 msec for both patients and control subjects. This effect was due to an increase in phase locking with increasing WM load (Figure 1B). This increased phase locking was evident at frontal and occipital electrode sites in both groups (Figure 1C; $p_{corr} < .005$). However, patients differed from control subjects, in that they showed generally reduced levels of alpha phase locking (Figure 1D; $p < .05$), which was evident over frontal and occipital electrode sites in each WM load condition (Figure 1E; $p_{corr} < .001$). There was no significant interaction between group and WM load (Figure 1E, right; $p_{corr} > .5$). This indicates that both groups showed a comparable increase in alpha phase locking with WM load. No significant differences between patients and control subjects were found in induced alpha power over parietal electrode sites (Figure S3 in Supplement 1).

Relation Between Alpha Phase Locking and Behavior

To clarify the functional significance of the alpha phase-locking effect in patients, correlation analyses between alpha phase locking

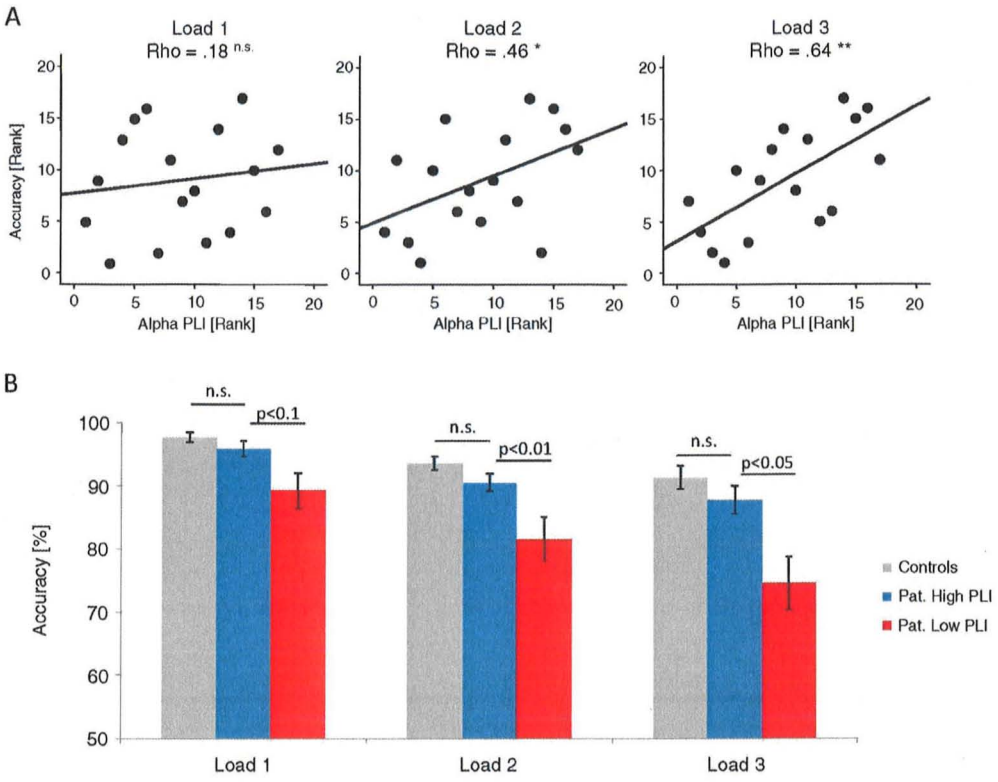

Figure 2. The relation between alpha Phase-Locking Index (PLI) and working memory (WM) performance for patients is shown. **(A)** The scatter plots depict the rank correlations between alpha PLI (x axis) and accuracy levels (y axis) for the three WM load conditions for patients. Correlations between alpha PLI and performance increase with WM load, with significant correlations being obtained for WM load 2 (*$p < .05$) and WM load 3 (**$p < .01$). **(B)** The accuracy levels across the three WM load conditions are shown for control subjects (gray), patients with high alpha PLI (blue), and patients with low alpha PLI (red). Error bars indicate mean SE. *P* levels were obtained by nonparametric Mann-Whitney tests. n.s., nonsignificant; Pat., patients.

and accuracy were conducted separately for each WM load condition. Figure 2A illustrates the increasing correlations between alpha phase locking and accuracy (load 1 < load 2 < load 3) being significant for WM load 2 ($p < .05$, rho = .46) and WM load 3 ($p < .005$, rho = .64). No correlations between phase locking and performance were observed for control subjects (rhos < .35; $ps > .15$), possibly because of low variability (consistently high performance) in the behavioral data.

To investigate this relationship further, the patients were split into a high and a low alpha phase-locking group based on the individual alpha phase-locking values at WM load 3. We compared the accuracy levels between control subjects and patients with high and with low alpha phase locking. As shown in Figure 2B, patients with high alpha phase locking demonstrated similar accuracy levels as control subjects in all three WM load conditions. In contrast, patients with low alpha phase locking showed significantly reduced accuracy in comparison with both control subjects and patients with high alpha phase locking at WM load 2 and WM load 3 (all $ps < .05$).

There were no correlations between medication level (chlorpromazine equivalent) and alpha phase locking.

Discussion

The present study shows that alpha phase locking may index a residually functioning mechanism, enabling patients with schizophrenia to encode visual stimuli into WM. This is supported by several points. First, patients demonstrated an increase in alpha phase locking with WM load, which was comparable with control subjects. Second, the enhanced alpha phase locking, with increasing WM load, predicted the ability of the patients to perform the task. Third, patients exhibiting high levels of alpha phase locking performed the WM task to a comparable level as control subjects.

Several studies have linked alpha oscillations to selective visual attention (e.g., [10]). These studies showed that alpha oscillations indicate a shift of spatial visual attention and predict visual perception (11). Thus, the WM load increase in alpha phase locking in schizophrenic patients suggests that the patients used visual attention mechanisms to boost encoding of the stimuli. This is supported by findings that the ability to orient spatial visual attention is generally intact in patients (12).

It has been suggested that alpha oscillations arise from synergistic interactions within thalamocortical reentrant networks (13), which may provide a temporal frame to gate perceptual events (14). Cholinergic activation of the thalamus produces alpha oscillations (15), and thus alpha oscillations may be engaged by both descending and ascending arousal systems (16). This indicates that visual attention may improve the timing of these networks, which renders the network more flexible to react to an external stimulus, and that the high-performing patients can still use these to boost encoding.

Several authors have described a relationship between alpha and gamma (> 30 Hz) phase locking (17). Interestingly, gamma-band activity, which has also been linked to working memory and attention, is reduced in schizophrenia (18) and can be boosted by cholinergic stimulation and arousal (19). Even though we did not observe gamma-band activity during encoding in response to the novel, unfamiliar stimuli, future studies may find similar effects in the gamma band.

Our results highlight the individual differences in cognitive function of patients with schizophrenia. Although our patient group, which was matched with control subjects for premorbid IQ, performed, on average, worse, the patient group with the higher alpha Phase-Locking Index performed similarly to control subjects. More research is needed to further characterize such high-performing schizophrenia patients neuropsychologically and neurophysiologically. A better understanding of the neural sources of cognitive deficits in schizophrenia may also have therapeutic implications. Interestingly, using transcranial magnetic stimulation at alpha frequency increased alpha power and decreased the amount of positive symptoms in schizophrenia (20). Our data suggest that strengthening alpha phase locking may also reduce the cognitive deficits in patients with schizophrenia.

CH is supported by the Wales Institute of Cognitive Neuroscience, funded by the Welsh Assembly Government.

The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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