Brief Report:

Alpha phase-locking predicts residual working memory performance in schizophrenia

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Abstract

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 mechanism.

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 controls and patients with high and low alpha phase-locking.

Results: Alpha phase-locking increased with WM memory load in both EOS and controls, 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 controls.

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.

Introduction

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 ERP component P1 as well as early evoked oscillatory activity (4-30 Hz) predicted successful WM encoding in controls, 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 show 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 (see supplementary methods). 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).

Whether there is also a relationship between alpha phase-locking and deficits in working memory encoding, however, is unclear to date.

In spite of 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, which enables the patients to perform the task. However, electrophysiological correlates of such residual mechanisms have not been described yet. Here we show that alpha phase-locking during encoding indexes working memory performance and is preserved in the high performing patients.

Methods and Materials:

Seventeen patients with early-onset schizophrenia (EOS) diagnosed according to DSM-IV criteria were compared to seventeen control participants matched for age, gender, handedness and premorbid IQ; for participants details see Haenschel et al, 2007). All patients were on medication at the time of testing with a mean chlorpromazine equivalent medication of 188.7 mg/d (SD 166). The study was approved by the ethics committee of the Medical School, Johann Wolfgang Goethe University, Frankfurt am Main, Germany.

A delayed discrimination task was implemented using the Experimental-Run-Time-System software (suppl. fig. 1). It probes load effects in visual WM with thirty-six 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. ERP and time frequency (but not phase-locking) analyses have been reported before (2, 3).

Recording, digitization and pre-processing of the 64-channel EEG data were carried out with a BrainAmp amplifier and the BrainVision Recorder software (Brain Products, Gilching, Germany). The EEG was recorded at a sampling rate of 500 Hz. Electrode impedance was kept below 5 kΩ. Only trials with correct responses were included. We analysed 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 (see suppl. Fig. 1). Phase-locking was calculated by means of the Phase-Locking-Index (PLI; (9). For a detailed description of the phase-locking analysis, and the statistical procedure see supplementary methods and supplementary figure 2.

Results:

Behavioral Results: As reported in Haenschel et al. (2007), patients exhibited reduced performance levels in the WM task compared to controls (group: $F_{(1,32)}=24.98$, $p<0.001$). 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 100-250 ms for both patients and controls. This effect was due to an increase in phase-locking with increasing WM load (fig. 1b). This increased phase-locking

was evident at frontal and occipital electrode sites in both groups (fig. 1c; $p_{corr}<0.005$). However, patients differed from control subjects, in that they showed generally reduced levels of alpha phase-locking (fig. 1d; $p<0.05$), which was evident over frontal and occipital electrode sites in each WM load condition (fig. 1e; $p_{corr}<0.001$). There was no significant interaction between group and WM load (fig. 1e, right; $p_{corr}>0.5$). This indicates that both groups showed a comparable increase in alpha phase-locking with WM load.

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 and accuracy were conducted for each WM load condition separately. Figure 2a illustrates the increasing correlations between alpha phase-locking and accuracy (L1<L2<L3), being significant for WM load 2 ($p<0.05$, Rho = .46) and WM load 3 ($p<0.005$, Rho = .64,). No correlations between phase-locking and performance were observed for control subjects (Rho's < .35; p's>0.15), 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 controls 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 controls in all three WM load conditions. In contrast, patients with low alpha phase-locking showed significantly reduced accuracy in comparison to both controls and patients with high alpha phase-locking at WM load 2 and WM load 3 (all p`s<0.05).

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 to controls. 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 controls.

Several previous 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 utilized visual attention mechanisms to boost encoding of the stimuli. This interpretation is supported by findings that the ability to orient spatial visual attention is generally intact in patients (see 12 for review).

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 utilize these to boost encoding.

Several authors have described a relationship between alpha and gamma (> 30 Hz) phase-locking (17). Interestingly, gamma-band activity 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 clearly argue against a model of generalized cognitive dysfunction in schizophrenia. Although EOS patients show impaired encoding, the present data suggest that they can to a degree utilize alpha phase-locking as a way to enhance performance. Interestingly, using TMS at alpha frequency increased alpha power and decreased the amount of positive symptoms in schizophrenia (20). Our data implicate that strengthening the alpha phase-locking may reduce cognitive deficits as well and may therefore have potentially important implications for the treatment of cognitive deficits (both behavioral and pharmacological).

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Figure Legends

Figure 1. The results of alpha phase-locking are plotted. (a) A time-frequency plot showing the difference in PLI between load 1 and load 3 is shown for controls (upper panel) and patients (lower panel). Red colors indicate stronger PLI in load 3 compared to load 1. (b) The time-course of alpha PLI is shown for the three WM load conditions. The dotted lines indicate the time-window which 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 non-parametric Friedman ANOVAs. Red colors indicate p-levels<0.05. P_{corr} refers to the p-level obtained by the randomization procedure (see supplementary methods). (d) The mean alpha PLI, averaged across the significant electrode sites (c), for the three WM load conditions is shown for controls (grey) and patients (black). Controls show higher levels of alpha PLI in each of the three WM load conditions (* $p<0.05$; ** $p<0.01$; nonparametric Mann-Whitney tests). Error bars indicate mean S.E. (e) The topographies indicate significant differences between controls 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 controls.

Figure 2. The relation between alpha PLI and 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 (* $p<0.05$), and WM load 3 (** $p<0.01$). (b) The accuracy levels across the three WM load conditions are shown for controls (grey), patients with high alpha PLI (blue), and patients with low alpha PLI (red). Error bars indicate mean S.E. P-levels were obtained by nonparametric Mann-Whitney tests.

Figure 1

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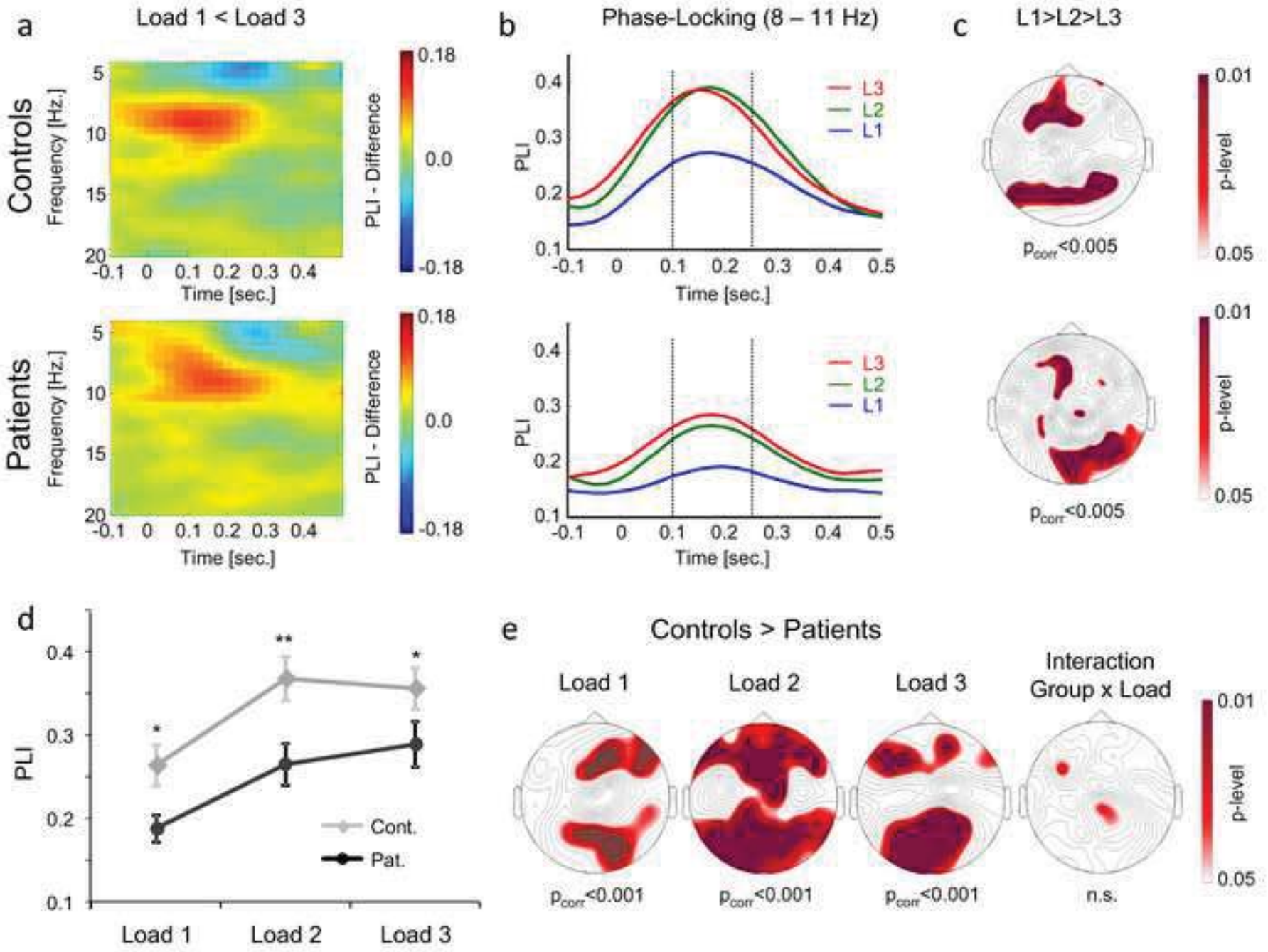

Figure 2

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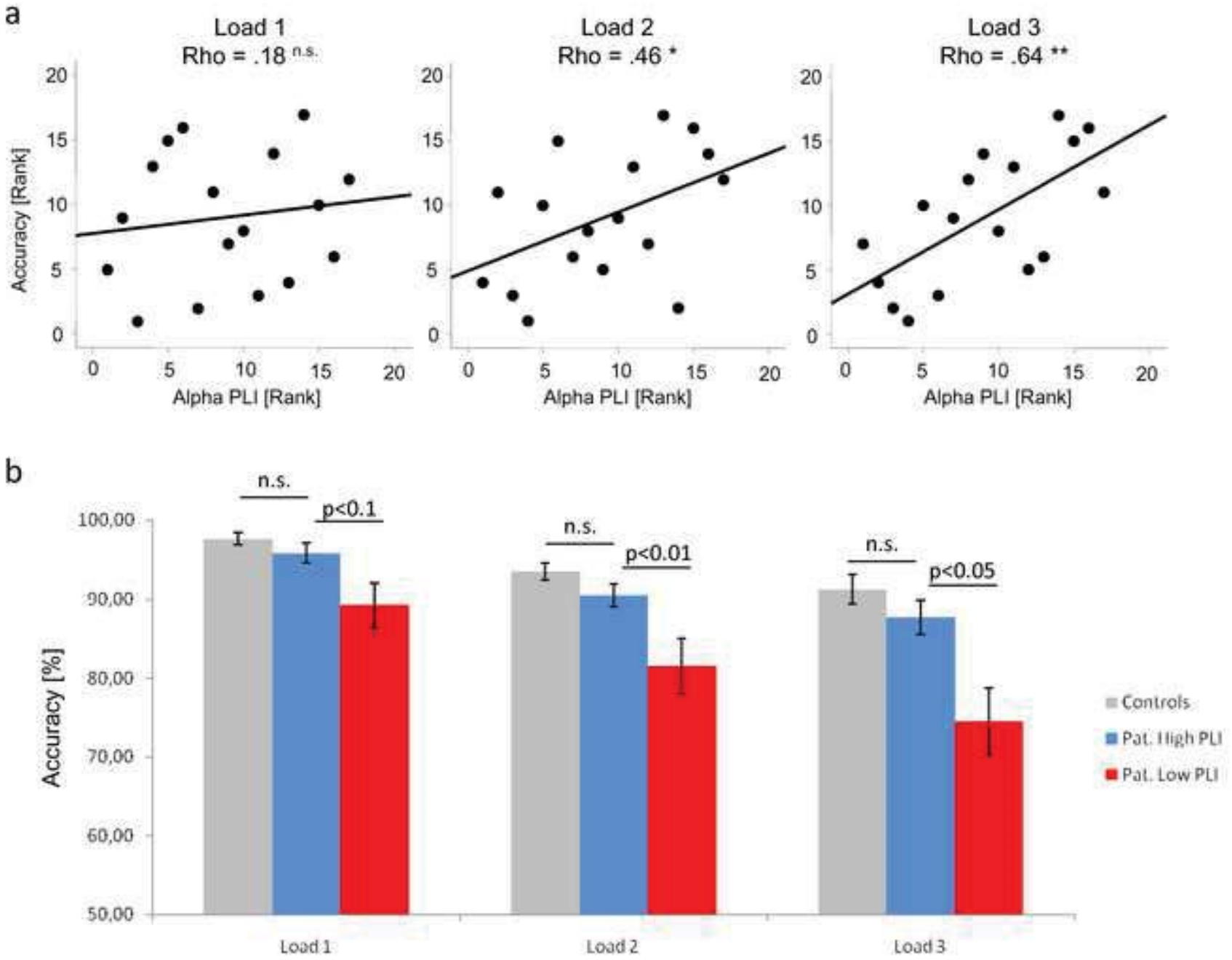

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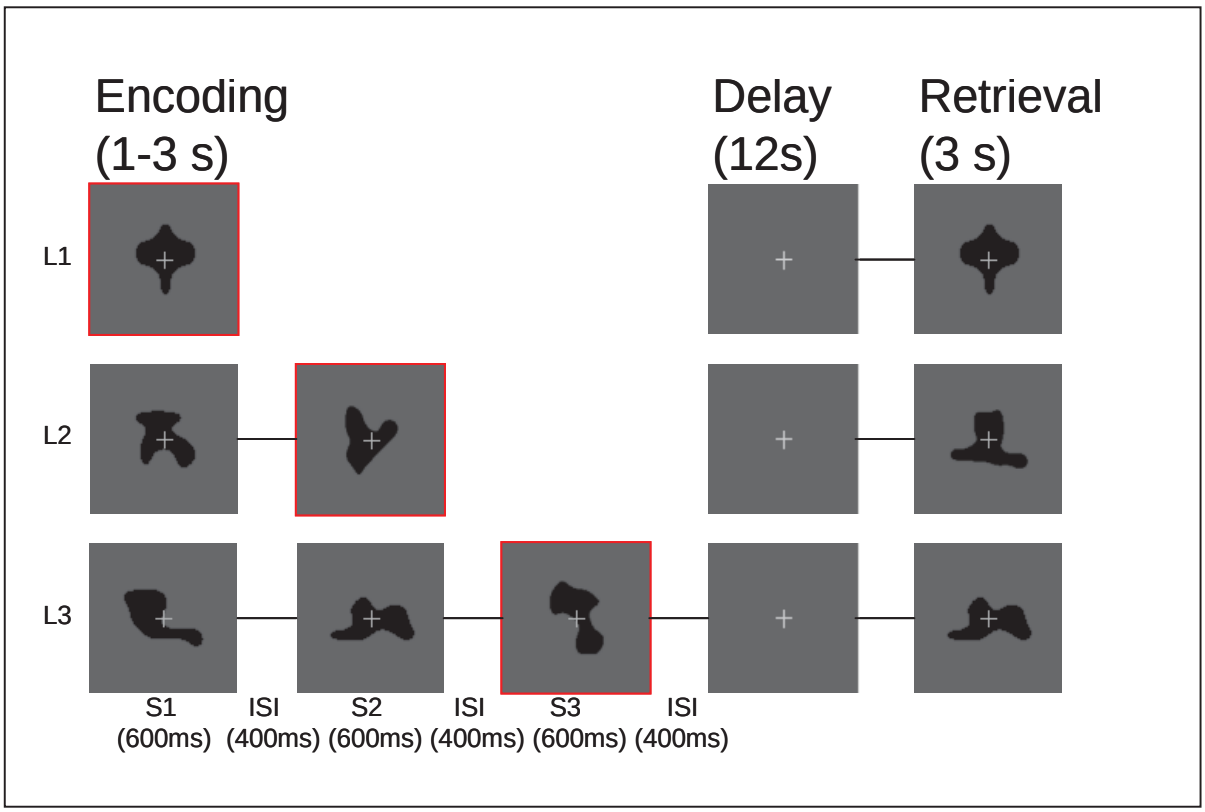
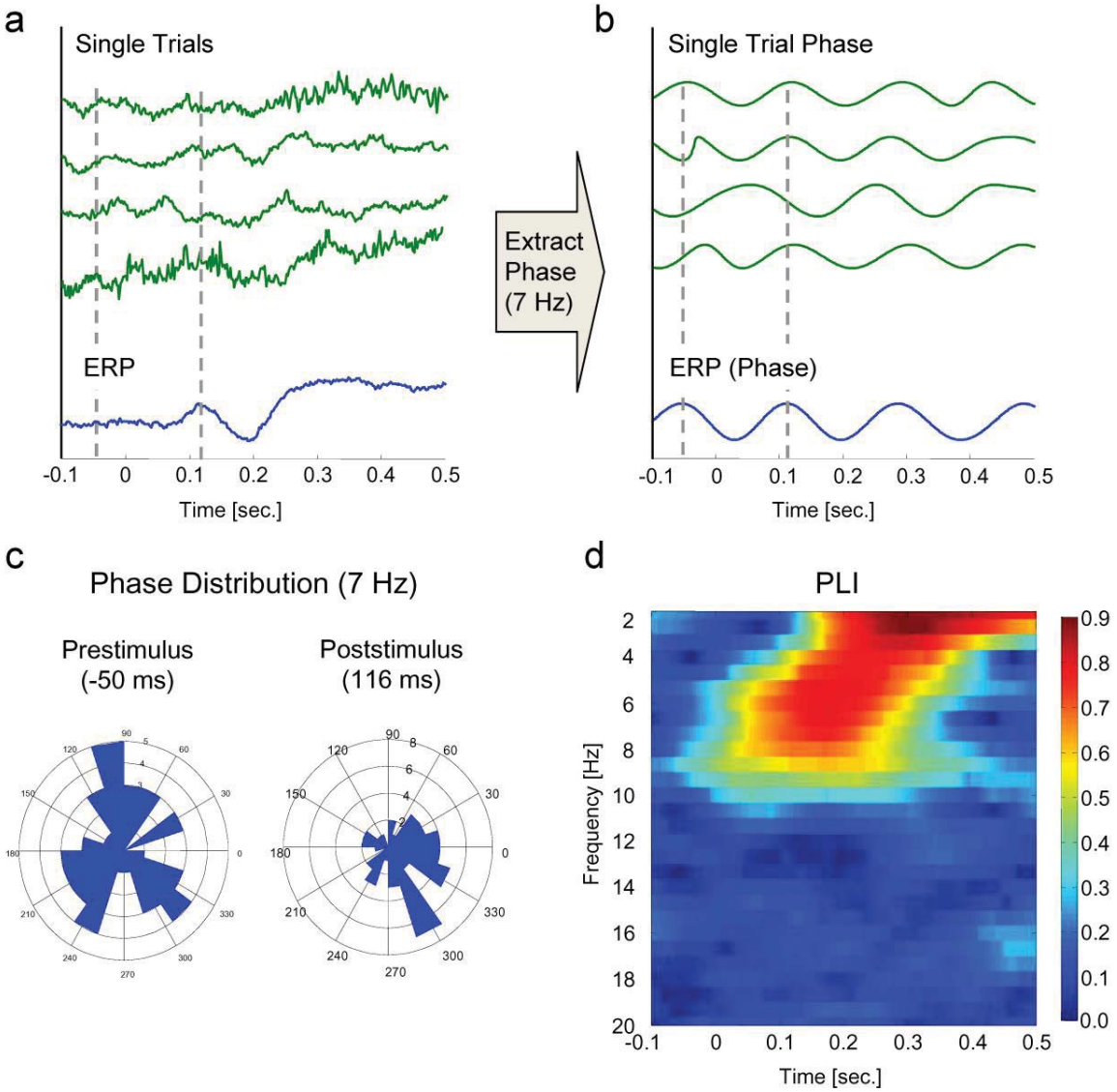
Supplementary Material

Supplementary Figure 1. In the visual delayed discrimination task WM load was varied by presenting one, two or three abstract shapes during encoding for 600 msec each with an interstimulus interval (ISI) of 400 msec. After a 12 second delay interval, a probe stimulus was presented for 3 seconds. Participants had to indicate by button press whether or not it was part of the initial sample set. The red frame indicates the inclusion of 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, into the analysis.

Supplementary Figure 2. The calculation of the phase-locking index is demonstrated for an occipital electrode (O2) of a single subject. The stimulus was shown at 0 ms. (a) Four single trials are plotted. The blue line indicates the ERP, averaged over all single trials (N=47). A pronounced P1 component can be seen at around 116 ms. (b) The real part (cosine) of the phase information at 7 Hz, of the four single trials (green), and the ERP (blue) is plotted. The dashed lines indicate a pre-stimulus time point (-50 ms), and a post-stimulus time point (116 ms). (c) The phase distribution of the pre-stimulus time point (-50 ms) and the post-stimulus time point (116 ms) is shown for all single trials. It can be seen that no phase alignment is evident 50 ms prior stimulus presentation, whereas strong phase alignment is observed 116 ms after stimulus presentation. (d) The time-frequency plot shows the phase-locking index (PLI), with warm colors indicating high phase-locking and cold colors indicating low phase-locking.



Supplementary Fig 1



Supplementary Fig 2

Supplementary Methods

Calculation of Phase-Locking: Phase-locking was examined using the phase-locking index (PLI). PLI is a measure of phase variability across single trials at a certain time point (Gruber et al., 2005), ranging from 0, indicating maximal phase variability, to 1, indicating perfect phase-locking (see suppl. fig. 2 for details). In contrast to evoked power measures, which retain both phase-locking and oscillatory amplitude, the PLI only retains phase information. Prior to filtering, the data were epoched from 500 ms pre, to 1000 ms post stimulus, retaining a frequency resolution of 0.66 Hz. Time-frequency transformation was calculated using Gabor wavelet analysis within a frequency range of 1 to 20 Hz. Prior to statistical analysis the PLI was collapsed according to the theta (4.33-7Hz), alpha (8.33-11Hz) and beta (12.33-19.66) frequency band. As no significant effects of WM load on the theta or the beta frequency band were obtained for patients, only results for alpha phase-locking will be reported. Statistical analysis of the mean values of alpha PLI was conducted between 100 to 250 ms post-stimulus as effects of load were strongest during that time window (fig. 1a).

Statistical Analysis: Statistical analyses were carried out using non-parametric randomization tests (see Hanslmayr et al., 2007; Hanslmayr et al., 2009 for details). To examine within subjects effects of WM load on PLI, non-parametric Friedman ANOVAs were calculated. To examine the difference in alpha PLI between patients and controls,

non-parametric Mann-Whitney-Tests were used. These tests were carried out for each of the 64 electrodes. To account for multiple testing, a 2-stage randomization procedure was carried out. At first, Friedman ANOVAs/Mann-Whitney-Tests, were calculated for each electrode to investigate how many electrodes exhibited a significant effect of group/WM load ($p<0.05$; 2-tailed). Thereafter, a randomization procedure using 2000 permutation runs was carried out, in which the assignments to conditions (load 1, 2 or 3) or group (patient/control) were interchanged randomly. The swapping of condition and group was done consistently across electrodes. After 2000 randomization runs, a distribution was generated, reflecting the number of electrodes which randomly showed significant differences. From this distribution the p-level of a given number of significant electrodes can be estimated. If the p-value (p_{corr}) of this randomization test is below 0.05, less than 5% of the permutation runs exhibited equal or more electrode sites with a significant difference.

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