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Alpha Oscillations underlie Working Memory Abnormalities in the Psychosis High-risk State

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Running title: Working memory in the psychosis high-risk state

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Word count in Abstract: 205

Word count in article body: 2998

Abstract

Background: Converging evidence suggests that working memory (WM) functioning, known to be modulated by neural oscillations, is impaired in schizophrenic psychoses. However, it remains unclear whether in the psychosis high-risk state, WM encoding is altered or whether patients are impaired at shielding their WM against distractors.

Methods: We employed single trial analyses of high-density neurophysiological and behavioral data recorded during a WM paradigm, designed to include predictable distractors, on 18 patients with an at-risk mental state for psychosis (ARMS) (26.1 +/-5.45 years) and 21 healthy controls (HCs) (25.5 +/- 3.95 years).

Results: Across groups, strong distractors were associated with reduced WM accuracy (p=0.036), but only ARMS patients required more processing time for strong distractors compared to weak distractors (p=0.002). On the neural level, increased parieto-occipital alpha amplitude immediately before distractor presentations was associated with enhanced accuracy in HCs (p=0.005) but not in ARMS (p>0.527). During encoding, increased intertrial alpha phase locking values were associated with increased accuracy and reduced reaction time across groups (p=0.001 and p=0.006, respectively).

Conclusions: Impairment in the shielding mechanisms against distractors in ARMS patients could lead to defective WM maintenance in ARMS patients. In complex environments, this could result in substantial confusion that may contribute to the formation of psychotic symptoms.

Keywords: neural oscillations; EEG; psychosis; schizophrenia; working memory; phase locking

Introduction

In an environment in which individuals are continuously bombarded with sensorial stimuli, it is essential to have effective mechanisms for filtering out irrelevant information (1, 2). These mechanisms could be partially implemented through alpha oscillations, which are known to be involved in gating of incoming information (3-6), and thereby preserve proper functioning of working memory (WM) (7-9). WM functioning, as well as the ability to gate sensory information, have repeatedly been shown to be impaired in schizophrenic psychoses (10, 11), suggesting that an alteration in alpha-oscillations could be a key mechanism in the pathogenesis of schizophrenic psychoses.

Over the past 20 years, numerous studies have assessed patients with a clinical high risk of developing psychosis to identify key mechanism in the pathogenesis of schizophrenia that would allow for an early intervention. These patients with an at-risk mental state (ARMS) for psychosis eventually develop psychosis within 3 years with a probability of about 36% (12, 13). These patients were found to have decreased P50 suppression in the sensory-gating ERP paradigm (14), suggesting that they have a poor "shielding" against internal noise and external distractors (1). That is, these patients could be highly sensitive to distractors, which would prevent them from having a well-functioning and stable WM (15). Alpha oscillations might be crucial for protecting the WM (16) against distractors as alpha oscillations in parieto-occipital brain regions in healthy human subjects were found to increase in anticipation of distractors and were directly correlated with increased performance in a WM task (2). Furthermore, phase-locked alpha oscillations have also been found to be associated with enhanced WM encoding and maintenance (2) with higher phase locking reported for better WM accuracy (17). Interestingly, Haenschel and colleagues (18) demonstrated that in schizophrenia, this neural mechanism seems to be disturbed and was associated with poorer WM encoding.

Therefore, applying a WM paradigm designed to also induce predictable distracting information, could allow us to assess whether ARMS patients demonstrate impaired WM performance partially due to disrupted alpha oscillations in anticipation of distractors. If so, these findings could point to a crucial mechanism in the pathogenesis of psychosis and could add to the prediction of psychosis when combined with other important predictors.

We thus aimed to investigate whether ARMS individuals demonstrate the mechanisms involving alpha oscillations that would allow for the suppression of anticipated obtrusive information. We used single trial analyses of high-density EEG recordings during a modified Sternberg task (2) (Figure 1A) in which participants could anticipate the strength and exact timing of distractors. This allowed us to investigate, on a single trial level, whethercompared to healthy controls (HCs), ARMS patients demonstrate decreased alpha oscillations prior to distractors which would be associated with lower performance as indexed by response accuracy and reaction-time (i.e., suggesting an inability to protect their WM against distractors). We also assessed whether in ARMS patients, the phase of alpha activity is still increased during encoding (letter presentation) and also associated with reduced task performance.

Methods

Setting and Recruitment

Our sample included 18 ARMS individuals and 21 HCs. All participants were recruited as part of the Basel ***F***rüh***er***kennung von ***Psy***chosen (***FePsy***) project, a prospective multilevel study aiming to improve the early detection of psychosis (19, 20). The study was approved by the Ethics committee of Northwestern and Central Switzerland. 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. Most participants were referred to the early detection clinic via the University of Basel Psychiatric Clinics or psychiatrists in private practice.

Some individuals were also referred from other physicians including general practitioners or came on their own due to extensive campaigns (See 20 for study design). 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. More details regarding neurological assessments of ARMS patients have been described elsewhere (21, 22).

Screening Procedure

The Basel Screening Instrument for Psychosis (BSIP) (23) was applied to identify ARMS individuals. The BSIP is largely based on the PACE inclusion/exclusion criteria (24) and has been shown to have a high predictive validity and a good interrater reliability (23). Exclusion criteria for patients were age<18 years, insufficient knowledge of German, low intelligence (IQ < 70), previous episode of schizophrenic psychosis treated with antipsychotics, psychosis clearly due to organic reasons or substance abuse, or psychotic symptoms within a clearly diagnosed affective psychosis or borderline personality disorder.

Assessment of Positive and Negative Psychotic Symptoms

The Brief Psychiatric Rating Scale Expanded (BPRS-E) (25, 26) was used to assess positive and negative psychotic symptoms. The positive psychotic symptom scale was based on the four 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. (27). We additionally assessed negative symptoms with the Scale for the Assessment of Negative Symptoms (SANS) (28).

EEG Task, Recordings and Analyses

We presented a modified version of the Sternberg task described in more detail by Bonnefond and Colleagues (2) (Figure 1A). We modified the timing of the stimuli of the task as follows:

following a fixation dot of 1500ms, a set of four consonants was serially displayed at a rate of 40ms with a blank screen of 1100ms between each letter. After the fourth blank screen, either a “weak” (a symbol) or “strong” (a consonant) distractor was presented for 40ms. Participants indicated by button press whether a subsequently appearing letter (known as the probe, the letter following the distractor) was part of the previous memory set (“old” or “new”). The participants could anticipate the distractor type because the weak and strong distractors were grouped in 2 sequential blocks resulting in 120 trials for each condition (i.e., 240 trials in total). The order of the distractors was randomized across individuals. Participants were explicitly asked to answer as fast as possible and to ignore the distractors. A short training session was performed before the actual recording to familiarize the subjects with the task.

Electroencephalography (EEG) recordings were made using BioSemi ActiveTwo electrode system with 64 scalp electrodes (BioSemi, Amsterdam, Netherlands) and digitized at 2048 Hz. Offline EEG data were resampled at 512Hz with a high-pass filter of .5Hz to attenuate channel drifts. Bad channels were interpolated using spherical splines, and eye movements and blinks were removed by applying the extended infomax independent component analysis algorithm. EEG data were low-pass filtered at 40 Hz. All trials were segmented separately from -5000 to 1000ms relative to stimulus onset (strong and weak distractors). Segments with activity exceeding ±80μV and gradients of 30μV/s were excluded from further analysis before averaging and re-referencing to the average reference. Brain activities were obtained from 2 regions of interest (ROI) of 5 symmetrical electrodes that revealed highest average amplitudes across all trials and groups on both the posterior left and right area (Figure 2A). The posterior left ROI consisted of electrodes P3, P5, P7, PO3 and PO7 and the posterior right ROI consisted of electrodes P4, P6, P8, PO4, PO8 (Figure 2B).

Wavelet and Intertrial Phase Locking Analyses

We examined oscillatory activities by means of wavelet decomposition. To calculate intertrial phase locking and single trial amplitude at 1 Hz frequency steps between 1 and 30 Hz, signals x(t) from each trial were convolved with a family of complex Morlet wavelets, $w(t, f_o) = A \exp(-t^2/2\sigma_t^2)\exp(2i\pi f_o t)$, where f_o is the central frequency, t is the time, and i is the imaginary part ($i = \sqrt{(-1)}$). Wavelets were normalized using the factor $A(w) = (\sigma_t\sqrt{(\pi)})^{-1/2}$. The family ratio, $m = f_o/\sigma_f = 5$, was used, where σ_f is the width of the Gaussian shape in the frequency domain. This ratio was used to optimize the trade-off between the temporal and frequency resolutions of the wavelet convolution (29). Amplitudes for each trial were subsequently averaged over single trials separately for all conditions. Single trial pre-distractor alpha activity [8-12Hz] was extracted from wavelets analyses from 400ms before the distractor for a total of 500ms.

To quantify the extent of normalized inter-trial phase variability across specific electrodes (30), the phase-locking value (PLV) was computed across trials for each electrode, at each time point (t), and frequency (f_o) yielding a PLV measure that ranges from completely randomized phases across sites (PLV = 0) at a specific time point to a consistent phase across electrodes (PLV = 1). Cumulated PLV is the sum of intertrial PLV elicited during the presentation of the four letters, that is, for each individual, we extracted the highest peak at -4560 to -3990, -3420 to -2850, -2280 to -1710 and -1140 to -570.

Statistical Analyses

Due the repeated measurement present in the data, the statistical analyses were performed using Generalized Linear Mixed effects models (GLME, for binary outcomes) and Linear Mixed Effects models (LME). We chose these models instead of the traditionally used repeated measures ANOVA, because they allow analyzing the data on a single trial level. Moreover, they can handle missing data more effectively and are more efficient, parsimonious, and flexible (31-33). Specific factors and models are defined in the Results section. P-values in LME models were estimated using Satterthwaite's approximation (34). Firstly, we assessed group differences by the number of correct responses (CR) in relation to distractor types on a single trial level. Secondly, we assessed how distractor type is related to reaction time (RT) across groups. Thirdly, we investigated the role of alpha amplitude (single trial pre-distractor alpha activity [8-12Hz] obtained from wavelets analyses from 400ms before the distractor for a total of 500ms) in protecting the WM against distractors by assessing the relationship between alpha activity and the probability of CR for both distractor types. This was also repeated for RT on correct responses. Fourthly, we assessed the role of intertrial PLV in the alpha band (8-12Hz, elicited during the presentation of each of the four letters) on RT. This was also repeated for alpha amplitude.

Results

Sample Description

Demographic and clinical characteristics are shown in Table 1. 18 ARMS patients (26.1 +/-5.45 years, 15 males) did not differ from the 21 HCs (25.5 +/- 3.95 years, 15 males) in terms of age, sex, years of education, non-verbal intelligence (LPS) and verbal intelligence (MWT-A).

Behavioral Analyses

A mixed effects logistic regression model using correct vs. incorrect as binary dependent variable, distractor type and group along with their interaction as fixed effects factors, and per subject randomly varying intercepts and distractor type slopes revealed a significant main effect of distractor type ($p<0.036$). That is, the strong distractor resulted in a lower probability of CR compared to the weak distractor independent of group (Figure 1B). The same model, but with log-transformed RT as dependent variable and a Gaussian error distribution, revealed significant main effects of distractor type ($p<0.001$) and group ($p=0.017$) and a significant distractor type × group interaction ($p=0.050$). Subgroup analyses revealed that distractor type was only significant for ARMS ($p=0.002$) and not for HC ($p=0.220$), indicating that strong distractors resulted in slower RT only in ARMS (Figure 1B).

Alpha Activity Analyses

An LME model with single trials pre-distractor alpha amplitude as dependent variable, group and distractor type along with their interactions as independent variables and per subject randomly varying intercepts and distractor type slopes, revealed no significant main effect of group, distractor or interaction effects (p=0.293 and p=0.971). These results show that the magnitude of pre-distractor alpha amplitude did not differ across groups.

LME model were fitted using cumulated intertrial alpha PLV (Figure 3A). LME model fitted with cumulated PLV during the letter presentation as dependent variable revealed a trend-level main effect of distractor (p=0.084) and distractor type × group interaction (p=0.108). Subgroup analyses revealed a significant distractor type effect in HC (p=0.047, Figure 3B) but not in ARMS (p=0.905). A same model with alpha amplitude during letter presentation, instead of alpha PLV, during letter presentation yielded no significant main effect of distractor type (p=0.533), group (p=0.573) or their interaction effect (p=0.884). These results suggest that during letter presentation, when expecting different distractor types, alpha PLV and not alpha amplitude are modulated differently in HCs only.

Single Trial Pre-distractor Alpha Activity and their Association with Behavioral Performance

A mixed effects logistic regression model using correct vs. incorrect as binary dependent variable, with pre-distractor alpha activity, distractor type and group along with their interactions as independent variables and per subject randomly varying intercepts and distractor type slopes revealed significant main effects of distractor type (p=0.036), and an interaction effect of pre-distractor alpha activity × group (p=0.009) (Figure 2C). Subgroup analyses revealed that this interaction was due to a significant main effects of pre-distractor alpha activity in HCs (p=0.005) and not in ARMS patients (p=0.527). These results illustrate that in HCs increased performance is strongly associated with increased pre-distractor alpha activity.

An analogous LME models with log-transformed RT with a Gaussian error distribution revealed significant main effects of pre-distractor alpha activity (p<.001), distractor type (p<0.001), group (p=0.018), and interaction effects of pre-distractor alpha activity × distractor type (p<0.001), Figure 2D. Sub-distractor analyses revealed that this interaction was due to a significant main effect of pre-distractor alpha activity in strong distractor (p<0.001) and not in weak ones (p=0.348). These results illustrate that pre-distractor alpha activity is associated with increased performance in RT across groups for strong distractors only.

Intertrial PLV and Alpha Amplitude during letter presentation and Behavioral Performance

A LME model using correct number of responses as dependent variable, cumulated intertrial alpha PLV during the presentation of each 4 letters, group and distractor type as independent variables along with their interactions and random intercepts per subjects, revealed a significant main effect of PLV (p=0.011) and a significant effect of group (p=0.021), Figure 3B. A similar model with alpha amplitude instead of alpha PLV during letter presentation yielded no significant main effect of alpha amplitude (p=0.771). That is, number of correct responses increased with increasing PLV, and not alpha amplitude, across groups.

The same model, but with log-transformed RT as dependent variable revealed a significant main effect of PLV (p=0.006) and an almost significant effect of distractor type (p=0.055), Figure 3C. A similar model with alpha amplitude instead of alpha PLV during letter presentation yielded no significant main effect of alpha amplitude (p=0.831). That is, RT decreased with increasing PLV across groups. Taken together, these results suggest that, across groups, alpha PLV elicited during letter presentation are associated with a higher performance as indexed by response accuracy and RT..

Discussion

The present study was designed to investigate whether the mechanisms involved in suppressing anticipated obtrusive information are still functioning in ARMS patients. In a task where participants could anticipate the strength and exact timing of distractors, we observed that across groups, strong distractors reduced WM accuracy. However, only ARMS patients required more processing time for strong distractors compared to weak distractors, which suggests that they are impaired in shielding WM against distractors. On the neural level, parieto-occipital alpha oscillations immediately before distractor presentations seem to be a crucial mechanism for shielding WM against distractors, a process which we hypothesized to be disrupted in ARMS patients. In support of this hypothesis, increased pre-distractor alpha amplitudes at parieto-occipital electrode sites were associated with enhanced processing speed for strong distractors across groups. However only in HCs was this activity associated with increased probability of correct responses. Unlike these disruptions during the time-range immediately before distractor presentation, during the encoding of the four letters, increased alpha phase locking values (PLV) was associated with increased WM performance across groups, suggesting that both groups show similar encoding processes in WM.

Converging evidence suggests that alpha oscillations are important for suppressing irrelevant information, leading to enhanced working memory performance (2, 35, 36). In particular, the timing and amplitude of alpha oscillations seem to be largely important in shielding the WM against distractors (2). In line with these findings, we revealed that increased pre-distractor alpha amplitude was associated with increased correct responses and decreased RT in HCs. ARMS patients showed increased RT for strong distractors and a lack of association between pre-distractor alpha amplitudes and probability of correct responses, suggesting that the WM in ARMS patients could be less shielded against irrelevant information. As a consequence, irrelevant information that is filtered-out by the healthy brain would be more deeply engrained and processed in ARMS patient (as reflected by a significant increase in RT in ARMS patients particularly for strong distractors). Although differences in processing speed (RT) could be observed in previous studies assessing patients with schizophrenia in several cognitive tasks (37-

39), similar findings are unclear in ARMS patients. That is, while generally lower task performance has been revealed in ARMS patients, processing speed differences in WM task are inconsistent (see (40) and (41) for relevant meta-analyses). It seems that the stronger distractor is more intrusive for WM performance in ARMS patients (as reflected by a significant group*distractor-type interaction), which could already be a sign of poor WM shielding or preservation commonly found in frank psychosis (42).

In addition to investigating the protective effects of alpha oscillations against intrusive stimuli, we have also assessed whether alpha oscillations are phase-synchronized, i.e., timed adequately during letter presentation. Alpha PLV is vital for visual information encoding in WM (17, 36), and have been found to be disturbed in schizophrenia along with associated cognitive deficits (18). In our study, increased PLV during letter presentation was associated with increased performance (i.e., increased correct responses and decreased mean RT) across both groups. Thus, in contrast to previous studies in schizophrenia, ARMS patients appear to still be capable of synchronizing and timing the phase of alpha oscillations during encoding.

Taken together, these results suggest that pre-distractor alpha amplitude and alpha PLV during letter presentations are associated with the preservation and encoding of WM leading to increased performance. In ARMS however, pre-distractor alpha activity was not associated with an increase in performance, suggesting an apparent inability to generate effective alpha activity when expecting distractors, leading to a fragile WM preservation. However, PLV of alpha oscillations during letter presentation suggest that their encoding capabilities are still intact.

Limitations

Noteworthy, differences in performance across groups cannot be attributed to different IQ as no differences were revealed in neither verbal nor nonverbal IQ tests (Table 1). However, the number of ARMS patients in this study is limited as these patients are relatively rare. Many of them only seek help when they have already developed frank psychosis; they are also reluctant to participate in scientific studies as they are quite suspicious at the beginning of the disease. Moreover, 5 of the 18 patients were medicated using antidepressants, which could have influenced the recorded brain activity. Thus, more studies are needed to replicate these findings using more patients and also investigate whether these findings can be confirmed using alternate experimental paradigms.

Conclusions

In a complex world in which ARMS patients are constantly bombarded with irrelevant stimuli, the lack of proper shielding mechanisms against distractors could lead to defective WM preservation, which could result in substantial confusion that may contribute to the formation of psychotic symptoms. These identified brain activity abnormalities could help to improve the prediction of psychosis and give new insights into the pathophysiological processes leading to the disease. Thus, they may help complement recent efforts targeted at early psychosis detection using multivariate pattern recognition techniques based on neural oscillations (43, 44).

Acknowledgements

The authors would like to thank Ulrike Heitz, Stephanie Menghini and Martina Uttinger for recruiting the patients. We would also like to thank the patients and volunteers for participating in this study. This study was supported by the Swiss National Science Foundation (grant numbers: P0BSP1-152074, 3200-057216.99, 3200-0572216.99, PBBSB-106936, 3232BO-119382).

Conflict of interest

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1: (A) The modified Sternberg task. Following a fixation dot of 1500ms, four consonants were sequentially presented at a rate of 40ms per letter. Between each of these four letters, a blank picture was presented for 1100ms. In the retention interval, either a ‘‘weak’’ (a symbol) or ‘‘strong’’ (a consonant) distractor was presented. Subjects indicated by button press whether the probe (the letter following the distractor) was part of the memory set (‘‘old’’ or ‘‘new’’). Participants could anticipate the distractor type as the weak and strong distractors were grouped in 4 blocks resulting in 120 trials for each condition (i.e., 240 trials in total). The order of the distractors was randomized across individuals.

(B) The hit rate and reactions times in response to the memory probe for each group. Although across both groups a lower correct response rate was observed for the strong distractor, the response times were significantly longer for the strong in patients only. This indicates in ARMS patients, strong distractors seem to be encoded more strongly in their working memory and interferes with retrieval processes. Error bars correspond to ±1 SE.

Figure 2: (A) Time-course of amplitude values for the strong and weak distractor condition and across groups (1 –30Hz). Red dashed lines represent the timing of each letter being presented and black dashed lines represent the timing of the distractors. (B) The scalp map depicting the electrodes studies in the current study. (C) Pre-distractor alpha amplitude as a function of reaction time across groups. (D) Pre-distractor alpha amplitude as a function of probability of correct response across groups. Shaded areas cover regression coefficients with ±1 SE.

Figure 3: (A) Time-course of alpha phase-locking values for the strong and weak distractor conditions and across groups (1–30Hz). Black dashed lines represent the timing of the distractors. (B) Phase-locking values elicited during letter encoding (4 letters) as a function of number of correct response for each group (C) Phase-locking values elicited during letter encoding (4 letters) and reaction time for each group. Shaded areas cover regression coefficients with ±1 SE.