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Abstract:

Impairments in working memory (WM) are a core cognitive deficit in schizophrenia. Neurophysiological models suggest that deficits during WM maintenance in schizophrenia may be explained by abnormalities in the GABA-ergic system, which will lead to deficits in high-frequency oscillations. However, it is not yet clear which of the three WM phases (encoding, maintenance, retrieval) are affected by dysfunctional oscillatory activity. We investigated the relationship between impairments in oscillatory activity in a broad frequency-range (3-100 Hz) and WM load in the different phases of working memory in 14 patients with early-onset schizophrenia and 14 matched control participants using a delayed matching to sample paradigm.

During encoding successful memorisation was predicted by evoked theta, alpha and beta oscillatory activity in controls. Patients showed severe reductions in the evoked activity in these frequency bands. During early WM maintenance, patients showed a comparable WM load-dependent increase in induced alpha and gamma activity to controls. In contrast, during the later maintenance phase patients showed a shift in the peak of induced gamma activity to the lower WM load conditions. Finally, induced theta and gamma activity were reduced in patients during retrieval.

Our findings suggest that the WM deficit in schizophrenia is associated with impaired oscillatory activity during all phases of the task and that the cortical storage system reaches its capacity limit at lower loads. Inability to maintain oscillatory activity in specific frequency bands could thus result in the information overload that may underlie both cognitive deficits and psychopathological symptoms of schizophrenia.

1. Introduction

Working memory (WM) deficits are a cardinal neuropsychological feature of schizophrenia (Tallon-Baudry et al., 1998; Goldman-Rakic, 2001; Silver et al., 2003; Gooding and Tallent, 2004). According to a previous meta-analysis, encoding and the early part of the maintenance seem to be the most affected subprocesses of WM (Lee and Park, 2005). Several behavioural studies have shown impaired performance in patients with schizophrenia linked to dysfunctional WM encoding (Javitt et al., 1997; Lencz et al., 2003; Lee and Park, 2005). Furthermore, we provided evidence that the ERP component P100 is of relevance for successful WM encoding in controls and is reduced in adolescent patients with schizophrenia (Haenschel et al., 2007b). WM maintenance deficits in schizophrenia have also been observed both behaviourally (Tek et al., 2002; Badcock et al., 2008) and using functional magnetic resonance imaging (fMRI) especially in the dorsolateral prefrontal cortex (DLPFC) **(Cannon et al., 2005; Lee et al., 2008) using spatial delayed response tasks.**

These neurophysiological and functional neuroimaging studies of visual WM have demonstrated that distinct cortical areas have particular importance for specific stages of WM. However, the underlying neurophysiological processes which link activity associated with WM within and across cortical areas still remain poorly understood. Synchronised high-frequency oscillatory activity may provide a flexible link to integrate neural activity within and between cortical areas, for a wide range of cognitive functions (Singer, 1999), including WM (Tallon-Baudry et al., 1998).

Such oscillatory activity is generated by networks of interconnected GABAergic interneurons (Whittington et al., 1995). Postmortem work in schizophrenia has shown reduced GABAergic and glutamatergic neurotransmission in certain DLPFC microcircuits (Lewis, 2000; Lewis and Moghaddam, 2006) and recently throughout the neocortex (Hashimoto et al., 2008). This should impair high-frequency oscillatory activity and could result in impaired perception and cognition. **Such a direct link between alterations in markers of GABAergic and glutamatergic neurotransmission and, in particular, gamma oscillatory activity has been found in animal models of schizophrenia (Cunningham et al., 2006; Roopun et al., 2008) demonstrating a deficit in gamma rhythmogenesis. Furthermore,** there is evidence of abnormal gamma band activity (30-100 Hz) in **human EEG** during both perceptual tasks (for instance Kwon et al., 1999; Spencer et al., 2003; Light et al., 2006) and WM maintenance (Cho et al., 2006; Basar-Eroglu et al., 2007) in patients with schizophrenia. In addition, abnormal oscillatory activity during WM has also been reported in the theta (3-7 Hz)

(Schmiedt et al., 2005) and alpha (8-12 Hz) (Bachman et al., 2008) frequency band (Haenschel et al., 2007a).

These WM studies used either a combination of cognitive control and N-back tasks (which makes it impossible to isolate the activity related to distinct WM subprocesses) or investigated only the delay period. Hence, the effects of oscillatory activity across *all* stages of a pure WM task and across longer delay periods still need to be investigated. Furthermore, the differences in frequency bands reported across the studies highlight the need to examine a wider range of frequencies in the same task.

The aim of the current study was to clarify which of the three WM phases (encoding, maintenance, retrieval) exhibit dysfunctional oscillatory activity in patients with schizophrenia and how these neural deficits would relate to the behavioural impairment. Finally, we examined whether oscillatory activity is reduced over a longer delay interval than has previously been investigated.

2. Materials and Methods

Subjects:

Fourteen patients with early-onset schizophrenia (EOS), i.e. an onset of the disorder before the age of 18, diagnosed according to DSM-IV criteria (9 males, 5 females; mean age: 17.76 (SD: 1.44); 11 right, 3 left handed, age at onset: 16,44 (SD: 1.24), illness duration: 1,26 (SD: 0.8), premorbid IQ: 97 (SD: 14)) using the Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 1995) and fourteen matched control participants (7 males, 7 females; mean age: 17.37 (SD: 1.41); 10 right, 4 left handed, premorbid IQ: 95 (SD: 8) underwent EEG recordings during a visual WM task. Current clinical symptoms of patients were assessed with the Positive and Negative Syndrome Scale (mean score: 43 (SD: 9.31) (Kay et al., 1987). All patients were on medication at the time of testing with 13 out of 14 receiving atypical antipsychotic medication (Quetiapine 10, Risperidone 1, Clozapine 1, Olanzapine 1). The mean equivalent medication level as measured in chlorpromazine equivalents (Woods, 2003) was 163.02 mg/d. One patient received selective serotonin reuptake inhibitors (SSRIs) as well. All adult participants provided informed consent prior to the study. In addition, for participants under 18 years, parents assented to participation. All participants with a history of substance abuse 6 month preceding the study or an additional neuropsychiatric diagnosis in the case of patients or any neuropsychiatric diagnoses in the case of controls were excluded.

Ethical approval was obtained from the ethics committee of the Medical School, Johann Wolfgang Goethe University, Frankfurt am Main, Germany.

Stimuli and Task

A delayed discrimination task that probes load effects in visual WM (Linden et al., 2003) with thirty-six non-natural visual objects (BORTS: blurred outlines of random tetris shapes) that were presented in the center of the computer monitor (visual angle, 1,34°) was implemented on a personal computer using the Experimental-Run-Time-System software (www.berisoft.com) (Fig. 1). BORTs have the advantage of being novel and difficult to verbalise. Two EEG sessions, each comprising three 10-minute blocks were held on consecutive days. Trials with different WM load levels were randomly distributed across sessions with a total of 50 trials obtained per WM load level. The ERP data have been reported previously (Haenschel et al., 2007b).

Figure 1 about here

Measurement and Analysis

A 64 channel electrode-cap was fitted to the participants' head with the ground electrode at position AFZ and the reference electrode at position FCZ. An additional vertical electrooculogram electrode was placed below the right eye. Electrode impedance was kept below 5 kΩ. Recording, digitization and preprocessing of the EEG data were carried out with a BrainAmp amplifier and the BrainVision Recorder software (Brain Products, Munich, Germany). The EEG was recorded at a sampling rate of 500 Hz with a system bandpass between 0-100 Hz.

EEG Data Analysis: EEG-data were referenced to linked electrodes TP9-TP10. This reference was chosen as it was unlikely to be involved in widespread synchronous activity (Rodriguez et al., 1999). Independent component analysis (ICA) was used to identify eyeblink artifacts by their distinct topography and to remove them from the data using the BrainVision Analyser software (Brain Products, Munich, Germany). Epochs were excluded automatically if the amplitudes exceeded a threshold of ±100 μV.

Following the recent report of Yuval-Greenberg et al. (2008; Melloni et al., 2009) the possibility of a relationship between induced gamma band activity and microsaccades must be

considered. We performed ICA decomposition and looked for components that (a) had the properties of microsaccades (irregular appearance over trials, broadband spectrum, frontal topography in average reference) and (b) accounted for the observed effects in the gamma band. We indeed found components with microsaccade-like properties (a), but these components exhibited power-time courses that differed from the observed effects in the gamma band. We concluded that induced gamma band activity in our data was not explained by microsaccades.

Encoding: To assess encoding, we only analysed the last sample stimulus in each WM load condition, i.e. the only stimulus for WM load 1, the second stimulus for WM load 2 and the third for WM load 3. This ensured an equal number of stimuli for each condition and more importantly, maximised the effect of prior processing in the higher WM load conditions. The baseline was –600 to 0 ms relative to trial onset followed by the analysis up to 3 s. For WM load 1 we analysed the first 1000 ms, for WM load 2 we analysed the time period between 1000 and 2000ms (1000 ms onset of stimulus 2) and for WM load 3 the period between 2000 ms and 3000ms (2000 ms onset of stimulus 3) following stimulus onset.

Maintenance: To assess maintenance, we defined two delay windows between 500 ms and 2500 ms and between 2500-4500 ms following stimulus offset. The baseline was –600 to 0 ms relative to the offset of stimulus 1, 2 and 3 for WM load 1, 2 and 3, respectively.

Retrieval: To assess retrieval related activity we set the baseline to –600 to 0 ms relative to the probe stimulus onset and we analysed the 1000 ms following the stimulus.

Following the segmentation, all correct trials were entered into the time-frequency analysis using Matlab scripts developed in-house, based on Lachaux et al. (1999). The digitized signals were analyzed by means of a windowed Fourier transform (window length: 150 points for the analysis of 10-100 Hz and 250 points for the analysis of 1-20 Hz, step 14 points, window overlap 90 %). Signal windows were zero padded to 512 points to obtain an interpolated frequency resolution of approximately one Hz per frequency bin. For every time window and frequency bin we computed amplitudes (see Uhlhaas et al, 2006 for methods).

In a second step we computed the evoked and the induced oscillatory activity over two regions of interest (ROI): 1) an anterior ROI: F1, FZ, F2, FC1, FCZ, FC2, C1, CZ, C2 and a posterior ROI: P3, PZ, P4, PO3, POZ, PO4, O1, Oz, O2. For the evoked activity we first averaged across the trials before computing the time-frequency plots, for the induced oscillatory activity we first computed the time-frequency distribution on single trials, subtracted the evoked part from the single-trials and finally averaged.

Statistical Analysis: Behavioral data were analysed with a 2-way Analysis of Variance (ANOVA) with the dependent variables reaction time and the estimated number of successfully encoded objects and the factors WM load and group. We computed the number of successfully encoded objects using Pashler's formula (Pashler, 1988; Cowan et al., 2005): s= n * (h-g)/(1-g) with s being the number of stored items, n the number of items in the display (1 in memory load 1, 2 in memory load 2, etc.), h the hit rate (correctly identified matches), and g the rate of false alarms (nonmatches incorrectly identified as matches).

The statistical analysis of EEG data was based on the assumption that encoding, early and late delay activity and retrieval would relate to oscillatory activity and may help to elucidate the differences between controls and schizophrenic patients. We analysed evoked and induced activity in the theta, alpha, beta and gamma frequency bands. In contrast to most previous studies, which focussed on a limited frequency range, we measured evoked and induced oscillatory activity for the full range between 3 and 100 Hz. We will, however, only report significant latency and amplitude effects.

During stimulus encoding we observed evoked beta activity (12-30Hz, analyzed between 30-350 ms following the onset of stimulus 1, 1030-1350 ms for stimulus 2 and 2030-2350 ms for stimulus 3), evoked alpha (8-12 Hz) and theta (3-7 Hz) activity (both analyzed between 30-500 ms following the onset of stimulus 1, 1030-500 ms for stimulus 2 and 2030-2500 ms for stimulus 3). During the first 5 seconds of the delay we observed induced alpha/beta activity (11-13 Hz) and induced gamma activity (55-100Hz) (both analyzed in an early delay interval between 500 ms and 2500 ms and in a later delay interval between 2500 ms and 4500 ms following stimulus offset). During retrieval we observed evoked theta activity (analyzed between 30 and 500 ms) followed by induced theta (analyzed between 200-600 ms) and gamma oscillatory activity (analyzed between 200 -800 ms).

Repeated measures multivariate analysis of variance (MANOVA) was used to test the effects within- ROI (9 anterior and 9 posterior electrodes) and WM load and between-participants (participant group) on all dependent mean amplitude and peak latency measures. We then analysed which of the subprocesses and which frequency components would best predict the estimated number of successfully encoded objects. This was addressed using multiple hierarchical regression with the estimated number of successfully encoded objects serving as the dependent variable and the evoked and induced frequency components for encoding, maintenance and retrieval in separate blocks serving as predictor variables. The

regression analysis was performed for each group separately. Furthermore, we correlated the chlorpromazine equivalents with the dependent measures.

3. Results

Behavior: Figure 2 shows the average reaction times and the number of successfully encoded objects for controls and patients. Reaction time increased with WM load for both groups ($F_{(2,25)}$=132.65, p<0.001). The control group demonstrated a greater increase with WM load than patients (load x group: $F_{(2,25)}$=3.53, p=0.041). The linear contrasts confirmed the monotonic increase in both groups with WM load ($F_{(1,26)}$=196.33, p<0.001).

The number of successfully encoded items was significantly lower for patients compared to controls ($F_{(1,26)}$=8.98, p=0.006). Both groups showed a linear increase of retained items with the increasing WM load ($F_{(1,26)}$=242,89, p<0.001), but the increase was stronger in controls compared to patients. This was statistically supported by a significant WM load x group interaction ($F_{(2,25)}$=4.4, p=0.027).

There was no correlation between chlorpromazine equivalents and reaction time or the number of successfully encoded objects.

Figure 2 about here

Time-frequency analysis of EEG signal energy

Encoding: The grand mean **evoked** beta, alpha and theta band activity at posterior electrodes in response to WM loads 1, 2, and 3 during encoding in controls and patients are illustrated in Figure 3.

The sample stimuli (i.e. stimulus 1 of WM load 1, stimulus 2 of WM load 2 and stimulus 3 of WM load 3) elicited evoked beta (12-30 Hz) between 30-350 ms post-stimulus and evoked theta (3-7 Hz) and alpha (8-12 Hz) band activity between 30-500 ms in both groups (table 1, supplementary material). Evoked alpha and theta band activity peaked earlier at posterior compared to anterior electrodes (alpha: $F_{(1,26)}$=7.97, p=0.009, theta: $F_{(1,26)}$=8.63, p=0.007). Evoked beta band activity did not show any difference in latency.

Patients showed reduced evoked theta ($F_{(1,26)}$=8.87, p=0.006), alpha ($F_{(1,26)}$=5.34, p=0.029) and in trend beta ($F_{(1,26)}$=3.93, p=0.058) band amplitudes compared to controls.

Furthermore, controls but not patients exhibited a decrease in evoked beta amplitude at posterior electrodes with increasing WM load (WM load x ROI x Group, $F_{(2,25)}$=4.9,

p=0.036). Evoked theta band showed a trend for an interaction between WM load and ROI (WM load x ROI: $F_{(2,25)}$=3.05, p=0.064). Post hoc tests indicated that evoked theta band activity decreased linearly in amplitude with increasing WM load in controls at posterior electrodes (WM load x group: $F_{(2,25)}$=6.3, p=0.019) similar to evoked beta band activity. In addition, evoked theta band activity exhibited a quadratic decrease at anterior electrodes for both groups ($F_{(2,25)}$=13.51, p=0.001).

Figure 3 about here

Given that evoked oscillatory activity in the delta to beta range has been associated with the early event-related P1-N1 components in healthy subjects (Klimesch et al., 2004; Gruber et al., 2005), we hypothesized that the deficits in evoked oscillatory activity in the theta, alpha and beta range reported here may be related to the P1 deficit in EOS patients as previously reported (Haenschel et al., 2007b). In order to test this hypothesis we performed post-hoc correlation between the P1 peak amplitude and the mean evoked theta, alpha and beta amplitudes. The results showed a significant positive correlation between P1 and posterior theta activity (r=0.41, p=0.007) in controls but not in patients. There were no significant correlations between P1 and evoked beta and alpha activity. There was no correlation between chlorpromazine equivalents and evoked oscillatory activity during encoding.

Delay: During the delay period we found significant changes compared to baseline in **induced** alpha and gamma band activity. Figure 4 depicts the grand mean induced alpha band at posterior electrodes and induced gamma band activity at anterior electrodes during the delay period of 500 ms to 4500 ms after stimulus offset. We divided the delay period into an early delay window between 500 ms and 2500 ms and into a late delay window between 2500 ms and 4500 ms (table 2, supplementary material). There were no significant differences in latency in induced alpha and gamma band activity during both delay periods.

Early Delay: The mean induced alpha band amplitude was significantly stronger at posterior electrodes compared to anterior electrodes ($F_{(1,26)}$=38.64, p<0.001), whereas the mean induced gamma band amplitude was in trend stronger at anterior electrodes ($F_{(1,26)}$=4.18, p=0.051). Patients and controls did not differ in induced alpha and gamma band activity. However, both groups showed an increase in induced alpha and in induced gamma band activity with increasing WM load (alpha: load: $F_{(2,25)}$=5.55, p=0.008, gamma: $F_{(2,25)}$=3.82, p=0.041). Post hoc tests confirmed that the increase with WM load was linear in induced gamma band

activity (linear increase: WM load ($F_{(1,26)}$=4.84, p=0.037) for both groups, but was only linear in controls for induced alpha band activity (linear increase: WM load x group ($F_{(2,25)}$=4.36, p=0.047). There was a negative correlation between chlorpromazine equivalents and induced alpha band activity for WM load 3 (r=-0.67, p=0.0012).

Late Delay: Similar to the early delay, induced alpha band activity was significantly stronger at posterior electrodes (F(1,26)=34.52, p<0.001), whereas induced gamma band activity was again stronger at anterior electrodes (F(1,26)=7.29, p=0.012). As for the early delay, neither induced alpha nor gamma band activity did differ between groups, but induced alpha band activity increased with increasing WM load ($F_{(2,25)}$=6.46, p=0.004) at posterior electrodes (WM load x ROI: $F_{(2,25)}$=4.55, p= 0.023, Figure 4). In contrast, induced gamma band activity showed an interaction between WM load x group that was in trend significant ($F_{(2,25)}$=2.97, p=0.079). Post hoc tests indicated that this may be attributable to a significant quadratic decrease (increase in induced gamma band activity for WM load 3) in controls and a quadratic increase (increase for WM load 2 followed by decrease for WM load 3) in patients with increasing WM load (linear contrast: WM load x group= $F_{(2,25)}$=11.44, p=0.002, Figure 4). There was no correlation between chlorpromazine equivalents and induced alpha and gamma band activity during late delay.

Figure 4 about here

Retrieval: In both groups the probe stimulus elicited **evoked** theta band activity between 30-500 ms and **induced** theta and gamma band activity between 200-600 ms and 200-800 ms, respectively (table 3, supplementary material). The grand mean evoked and induced theta band activity at anterior electrodes and induced gamma band activity at posterior electrodes in response to WM loads 1, 2, and 3 during retrieval in controls and patients are illustrated in Figure 5.

Evoked activity: Evoked theta band activity did not show any difference in latency and there was no significant amplitude difference between anterior and posterior electrodes. Patients showed significant mean amplitude reductions in evoked theta band activity ($F_{(1,26)}$=6.63, p=0.016). There were no further differences between WM load conditions for evoked theta band activity.

Induced activity: Induced theta band activity peaked earlier at posterior compared to anterior electrodes ($F_{(1,26)}$=8.15, p=0.008), whereas induced gamma band activity did not show any difference in latency.

The mean induced theta band activity was significantly stronger in amplitude at anterior electrodes ($F_{(1,26)}$=58.93, p<0.001) and the mean induced gamma band activity was significantly stronger at posterior electrodes ($F_{(1,26)}$=16.85, p<0.001). Both induced theta ($F_{(1,26)}$=9.28, p=0.005) and gamma band ($F_{(1,26)}$=5.22, p=0.03) activity were reduced in patients compared to controls.

Finally, the mean amplitude of induced theta band activity decreased with the increase in WM load ($F_{(1,26)}$=5.28, p=0.01) in both groups. This was explained by a quadratic decrease at posterior electrodes (WM load x ROI: $F_{(2,25)}$=9.45, p=0.001). There was no WM load effect on induced gamma band activity.

Figure 5 about here

Correlation between behavioural data and frequency components:

Hierarchical linear regression analyses were computed for frequency bands that either showed a group or a WM load effect in order to test if the number of successfully encoded items can be predicted by any of the frequency components during encoding (block 1: evoked posterior beta, evoked posterior alpha and evoked anterior theta), during delay (block 2: induced early and late delay anterior gamma and induced early and late posterior alpha) and during retrieval (block 3: evoked and induced anterior theta and induced posterior gamma activity). Only activity during encoding but not during delay or the retrieval period predicted the number of successfully memorised items. During encoding evoked posterior beta, alpha and anterior theta band activity ($F_{(2,25)}$=6.91, p=0.001, R^2: 0.35) predicted the number of successfully encoded items in controls but not in patients. Whereas the number of encoded items was negatively correlated with evoked beta and theta band activity (standardized β: -0.590, p<0.001 and standardized β: -0.301, p=0.031, respectively), it was positively correlated with evoked alpha band activity (standardized β: 0.449, p=0.005).

Discussion

This study investigated evoked and induced oscillatory EEG activity in a broad frequency range in patients with EOS and healthy controls during the three phases of visual WM.

Compared to controls, patients showed changes in oscillatory activity in all the three phases of a visual WM task. In controls, evoked activity in theta, alpha and beta band activity during encoding predicted the number of successfully encoded items. Patients showed reduced evoked activity in these frequency bands. During the late maintenance period patients showed an increase of induced gamma band amplitude in response to WM load 2 and failed to sustain induced gamma band activity for the highest WM load. In contrast, controls showed an increase in induced band gamma amplitude in response to WM load 3. This is consistent with patients experiencing difficulties in WM tasks already at lower memory loads.

Encoding:

During encoding patients showed reduced evoked oscillatory activity in a frequency range between 3-30 Hz (theta, alpha and beta band activity) compared to controls.

Using hierarchical regression including encoding, maintenance and retrieval in separate blocks we found that only WM encoding activity significantly predicted performance. Such a relationship was only found for the control group.

Impairments in evoked oscillatory activity may be explained by a reduced precision in the transmission of transient signals, and thus by a reduced signal-to-noise ratio. Alternatively, a reduction in stimulus-induced phase resetting of ongoing rhythmic activity in each trial may lead to impairments in evoked oscillatory and the P1/N1 complex (Makeig et al., 2002; Klimesch et al., 2007). Thus, the deficits in evoked oscillatory activity in the patients may be related to the recent finding of a P1 deficit during WM encoding (Haenschel et al., 2007b). This interpretation is supported by the present finding of a relationship between posterior theta activity and the P1 component in controls but not in patients.

Controls showed a decrease in evoked theta and beta activity with increasing WM load, whereas patients showed a general reduction compared to controls and no changes with WM load.

The reduction of evoked beta band activity with increasing WM load in controls could be due to a strong response to the first stimulus followed by habituation in response to the second and the third stimulus (Haenschel et al., 2000). In that case the reduced evoked beta band activity in patients may be attributable to an inability to entrain the neural system to the first item in a sequence of stimuli. A similar inability to respond to the first stimulus with an increase in

evoked theta and beta band activity and to habituate to the second stimulus has been found in auditory sensory gating studies (Hong et al., 2004a; Jansen et al., 2004; Brockhaus-Dumke et al., 2008).

It is of interest to note that there is increasing evidence for some degree of independence of the local circuits and mechanisms underlying beta 1 (12-20 Hz) and beta 2 (20-30 Hz) (Roopun et al, 2008), which may also be reflected in some differences in their cognitive functions (Uhlhaas et al., 2008). However, post-hoc analysis separating the power changes in the beta1 and beta2 subbands found no significant modulation across conditions, which suggest that the effects reported above were more widely distributed across the beta band range.

Early delay:

Contrary to Lee & Park's (2005) proposal, we did not observe any group difference in the early delay activity. The increase of induced alpha and gamma band activity during the delay period in association with WM load complements previous findings of working memory maintenance-related oscillatory activity (Tallon-Baudry et al., 1998; Jensen et al., 2002; Busch and Herrmann, 2003; Howard et al., 2003; Leiberg et al., 2006). In addition, increased induced gamma band activity has been described during the short-term consolidation of letters into WM that lasted for several hundred milliseconds (Mainy et al., 2007) and during maintenance reflecting the sustained activity necessary for stimulus feature representations (Kaiser et al., 2008). This may indicate that both groups used the same resources for the short-term consolidation and early maintenance of the stimulus representations in WM. Interestingly, Fuller et al. (2005; 2009) provided behavioural evidence that the consolidation of perceptual representations in WM is slowed in patients with schizophrenia. Our results would suggest that this is primarily due to impairments in evoked oscillations during encoding resulting in less salient (i.e. noisier) perceptual representations which impair WM consolidation.

Late delay:

Most of the previous EEG studies of WM used a much shorter delay between the sample and probe stimuli, and were thus not able to capture any differential processes during prolonged delay periods (see Meltzer et al., 2008 for a 6s delay window). Induced gamma band activity in the later delay window showed a trend towards divergent patterns of activity between the groups, with an increase in induced gamma band activity from WM load 2 to 3 in controls and

from WM load 1 to 2 in patients and a decrease from WM load 2 to 3 in patients. Interestingly, Basar-Eroglu (2007) also reported hyperactivation of evoked gamma band activity for lower WM task demands in patients in a combined cognitive control and N-back task. The U-shaped function of load-dependent gamma activity of the patients also bears intriguing resemblance to similar fMRI findings (Callicott et al., 2003; Karlsgodt et al., 2009), which indicate that the cortical storage system reaches its limit at lower WM demands. This interpretation is supported by the interaction between WM load and group in our behavioural data. However, due to the poor spatial resolution of EEG, this pattern could be explained by the mean of all sources contributing to the induced gamma band activity.

The inverted U-shape pattern only emerged during the later part of the delay, which is consistent with the observation by Reilly et al. (2006) that spatial WM deficits of patients became apparent only at longer delay periods (from 3 s to the maximum impairments at 8 seconds). Further studies with such long delay periods are needed for an understanding of the mechanisms of WM rehearsal and decay.

Retrieval:

Compared to controls, patients showed reduced evoked and induced theta and induced gamma band activity during retrieval. Given that induced theta band activity is larger for old compared to new words during recognition (Klimesch et al., 1997), this could be an indication that controls recognised the previously stored items, whereas patients might have treated them as novel. Induced gamma band activity has been suggested to be a signature of cortical object representation and an increase in induced gamma band activity over posterior electrodes has been linked to successful recognition of complex meaningful objects (Gruber and Muller, 2005; Lachaux et al., 2005; Gruber and Muller, 2006). The reduction of induced gamma band activity, thus, suggests that during retrieval patients were less able to retrieve the representation from WM. However, our data did not show a relationship between the amount of induced gamma activity during retrieval and successful recognition: Whereas the group difference in induced gamma band activity was already evident in patients for WM load 1, behaviourally patients were equally successful for this WM load.

A limitation of this study is that all the patients were receiving medication at the time of testing. However, the fact that we found no correlation with individual chlorpromazine equivalents in line with previous studies on oscillatory activity (Gallinat et al., 2004; Hong et

al., 2004b) in schizophrenia suggest that the impairments in oscillatory activity in our sample of patients with EOS are unlikely to reflect the effects of medication.

Furthermore, because we studied a group of adolescent patients with a relatively recent onset of illness, factors like long illness duration, chronic medication and higher sample heterogeneity should have confounded our study to a lesser degree than the majority of studies investigating adult patients with chronic schizophrenia.

We would thus suggest that changes in oscillatory EEG activity reflect some of the neurodevelopmental processes leading to schizophrenia. Such a neurodevelopmental account has also been suggested for the putative underlying neurochemical and local circuit changes (Lewis and González-Burgos, 2008; Uhlhaas et al., in press). However, we do not exclude that the progression of the disease is characterized by additional neural changes that lead to further impairments of neural synchronization, which has indeed been suggested by a recent study that compared induced high-frequency oscillatory activity during the perception of Mooney faces in controls, first-episode and chronic patients. This study reported a progressive deficit in oscillatory activity during the course of the disorder (Tillmann et al., 2008).

General Conclusions and Implications

The design of our study, which included the parametric manipulation of WM load and a long delay interval, allowed us to extend previous work on the relationship between oscillatory activity and WM impairments in schizophrenia in several ways. First, our results indicate impairments in all WM phases in a broad frequency range, whereas previous studies mostly focused on WM maintenance. This highlights the importance of investigating the contribution of the different WM phases to performance.

Second, the analysis of a 5 s delay period suggests that impairments in oscillatory activity may become more evident during longer maintenance intervals. One possibility is that during longer maintenance additional processes related to active rehearsal may become important which may be more susceptible to disturbance in patients with schizophrenia. Finally, the missing relationship between evoked activity and performance in patients indicates the functional significance of early evoked oscillatory impairments during encoding for the understanding of the disorder.

This raises the question if evoked oscillatory activity may in future be used to asses treatment response and may serve as a tool in early diagnosis. Furthermore, our results have potentially

important implications for cognitive rehabilitation programs. Cognitive remediation therapy has been associated with moderate improvements in working memory (Wykes et al., 2007a; Wykes et al., 2007b) as measured with the Digit Span. Our present and previous (Uhlhaas et al., 2006; Haenschel et al., 2007b) data suggest that additional visual perceptual training may enhance these effects.

Our results also have implications for the pathophysiology of schizophrenia. Lewis (2000) suggested that altered GABA neurotransmission in the DLPFC may lead to impaired oscillatory activity and as a consequence to WM deficits. Hashimoto et al. (2008) have now extended the finding of altered GABA neurotransmission to multiple cortical regions including primary visual cortices. **Indeed, by now there is evidence that alteration in markers of the GABA system and deficits in NMDA receptor-mediated excitation of these interneurons result in patho-rhythmogenesis within specific frequency bands using animal models of schizophrenia (Cunningham et al., 2006; Roopun et al., 2008). Our finding of widespread reduced evoked oscillatory activity during WM encoding may thus relate to such altered GABAergic neurotransmission and abnormal NMDA receptor-mediated glutamatergic inputs onto these GABA neurons (Lewis and Moghaddam, 2006).** Oscillatory EEG (and MEG) activity is probably the only non-invasive neurophysiological measure that allows for direct comparison with neuronal firing models (Whittington et al., 1997; Doheny et al., 2000; Haenschel et al., 2000) and is thus uniquely suited for the translational testing of molecular and cellular models of schizophrenia.

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Figure legends:

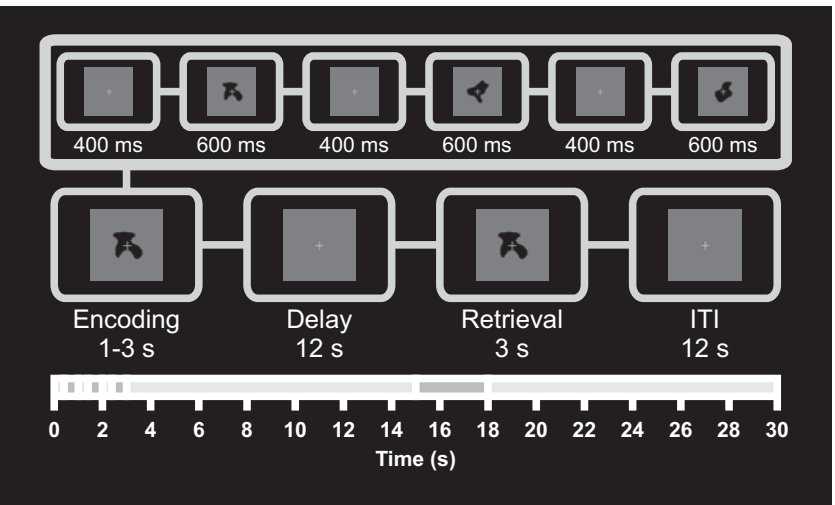
Figure 1. Working Memory Paradigm. The visual delayed discrimination task using abstract shapes. WM load was varied by presenting either one, two or three objects for encoding for 600 msec each with an interstimulus interval of 400 msec. After a 12 second delay interval, a probe stimulus was presented for 3 seconds. Participants had to judge whether or not it was part of the initial sample set by pressing a button. The intertrial interval was 12 seconds.

Figure 2. Figure 2. Behavioural Data (Reaction Time and Number of successfully encoded items).
Mean Reaction Time (top row) and Number of successfully encoded items (bottom row) in response to WM load of 1, 2 or 3 in controls (black line) and patients (grey line). Error bars represent standard error (SE).

Fig 3. Evoked oscillatory activity during WM encoding.
Evoked beta (top), alpha (middle) and theta (bottom) activity following WM load 1 (left), WM load 2 (center) and WM load 3 (right) are shown for the encoding period of 3s at posterior electrodes for controls (top row) and patients with early-onset schizophrenia (middle row) and the group comparison in the frequency range and time window of interest (bottom row, NC: normal controls shown in blue and EOS: patients with early-onset schizophrenia shown in red). The frequency range and the window of interest (the first sample stimulus for WM load 1, the second stimulus for WM load 2 and the third stimulus for WM load 3are denoted in bars). On the far right mean amplitudes in response to WM load 1, 2 or 3 are shown for the anterior and posterior ROI for patients with EOS (EOS, red) and controls (NC; blue). Error bars represent SE.

Fig 4. Induced oscillatory activity during WM maintenance.
Induced alpha (top) at posterior electrodes and gamma activity (bottom) activity at anterior electrodes during the maintenance following the offset of the first sample stimulus for WM load 1 (left), the offset of the second stimulus for WM load 2 (center) and the offset of the third stimulus for WM load 3 (right) are shown for the early delay (500-2500 ms) and the late delay (2500-4500 ms) period for controls (top row) and patients with early-onset schizophrenia (middle row) and the group comparison in the frequency range of interest (bottom row, NC: normal controls shown in blue and EOS: patients with early-onset schizophrenia shown in red). On the far right mean amplitudes in response to WM load 1, 2 or 3 during early and late delay are shown for the anterior and posterior ROI for patients (EOS, red) and controls (NC; blue). Error bars represent SE.

Fig 5. Induced oscillatory activity during WM retrieval.
Evoked (top) and induced theta (middle) at anterior electrodes and induced gamma (bottom) activity at posterior electrodes following the test stimulus for WM load 1 (left), WM load 2 (center) and WM load 3 (right) are shown for the retrieval period of 1s for controls (top row) and patients with early-onset schizophrenia (middle row) and the group comparison in the frequency range and time window of interest (bottom row, NC: normal controls shown in blue and EOS: patients with early-onset schizophrenia shown in red). The frequency and latency range of interest are denoted in bars. On the far right mean amplitudes in response to WM load 1, 2 or 3 are shown for the anterior and posterior ROI for patients (EOS, red) and controls (NC; blue). Error bars represent SE.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Delay
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Retrieval
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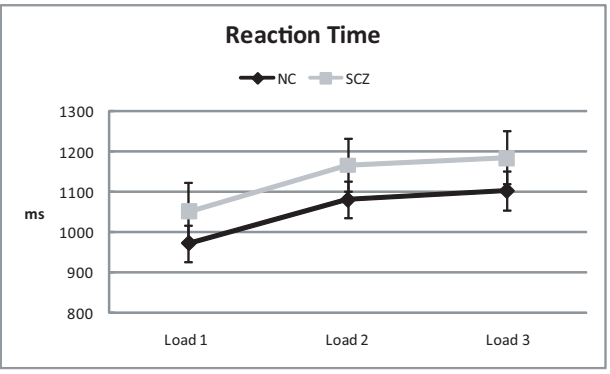
Time (s)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SCZ
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1100
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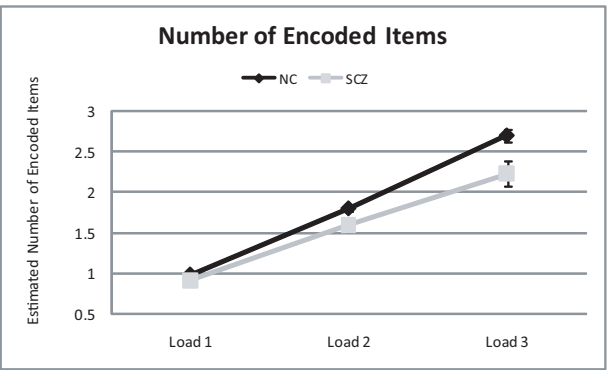
ms
Load 1
Load 2
Load 3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SCZ
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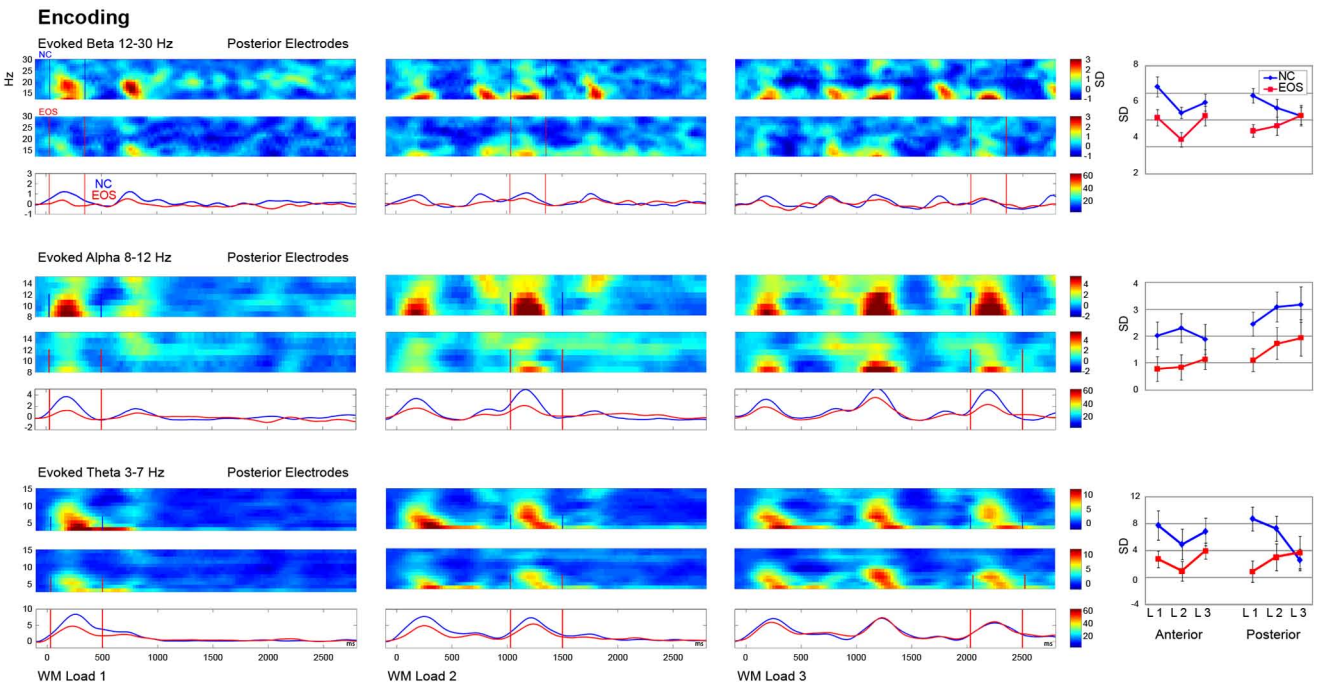
2
1.5
1
0.5
Estimated Number of Encoded Items
Load 1
Load 2
Load 3


Encoding
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Posterior Electrodes
Hz
NC
EOS
SD
Evoked Alpha 8-12 Hz
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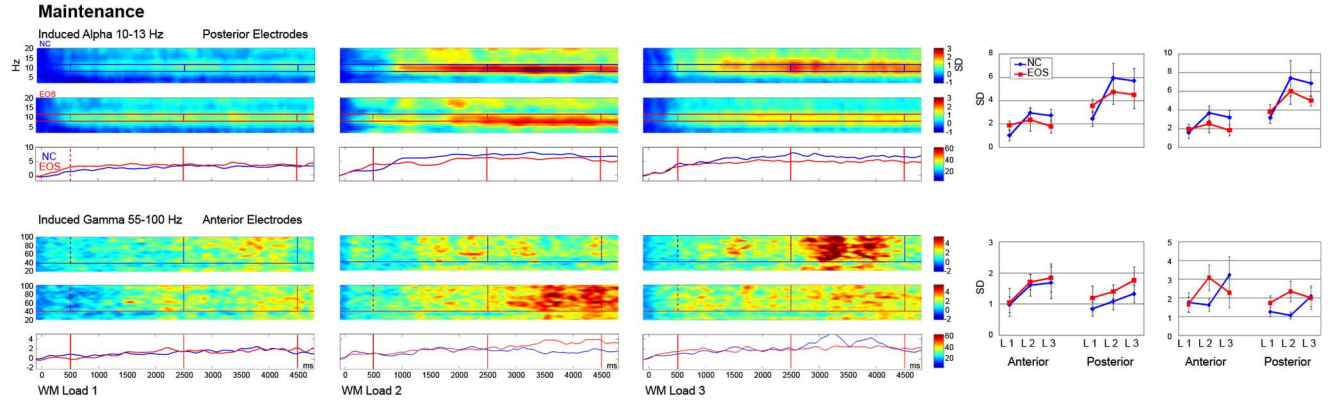
ms
L 1 L 2 L 3
Anterior
Posterior
WM Load 1
WM Load 2
WM Load 3


Maintenance
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Hz
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Induced Gamma 55-100 Hz
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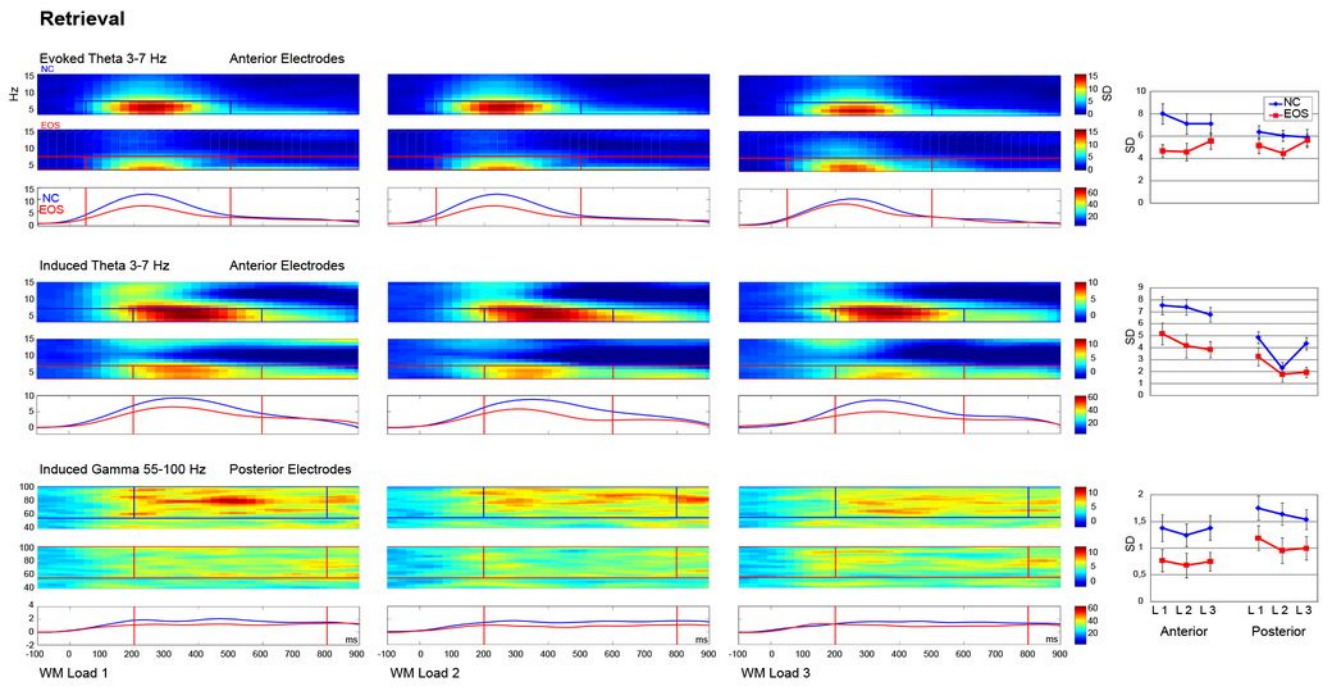
L1 L2 L3
Anterior
Posterior


Retrieval
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NC
EOS
Hz
SD
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ms
L 1 L 2 L 3
Anterior
Posterior
WM Load 1
WM Load 2
WM Load 3