Neurobiology of Learning and Memory 93 (2010) 208–215

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Human frontal midline theta and its synchronization to gamma during a verbal delayed match to sample task

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ARTICLE INFO

Article history:
Received 26 February 2009
Revised 23 September 2009
Accepted 29 September 2009
Available online 4 October 2009

Keywords:
Cross-frequency interaction
Electroencephalogram (EEG)
Executive processes
Phase locking
Retention

ABSTRACT

The involvement of oscillatory activity, especially at theta and gamma frequency, in human working memory has been reported frequently. A salient pattern during working memory is electroencephalographic frontal midline theta activity which has been suggested to reflect monitoring functions in order to deal with a task. In general, theta activity has been credited with integrative functions of distributed activity. In the present study, we focused on electroencephalographic power analyses and cross-frequency phase synchronization in order to test whether frontal midline theta activity is linked to more locally generated gamma oscillations during the performance of a verbal delayed match to sample task. The task consisted of two different conditions where subjects either had to reorganize three consonant letters in alphabetical order (manipulation condition) or where they merely had to retain the three consonant letters (retention condition). Results revealed higher frontal midline theta activity for the manipulation of maintained stimulus material compared to pure retention of stimulus material. Interestingly, power differences between conditions were most pronounced during the second half of the delay period. Cross-frequency phase synchronization between frontal midline theta activity and distributed gamma activity, on the other hand, was predominant during the first half of the delay period and was stronger for manipulation compared to retention. We suggest that coupling of frontal midline theta to gamma activity reflects monitoring functions on the temporal segregation of memory items, whereas higher frontal midline theta power in the second half of the delay period might be associated with rehearsal processes. Rehearsal processes in the manipulation condition are likely more pronounced, because rehearsal of a new letter string in a limited time window requires higher mental effort compared to pure retention where rehearsal processes may already start at the beginning of the delay period.

1. Introduction

Electroencephalographic (EEG) frontal midline theta (FM-theta) activity has long been discussed in association with working memory (WM) processes in humans. FM-theta activity is rhythmic activity in the 4–6 Hz frequency range which reaches its maximum at frontal midline electrode positions (Fz, F3 and F4) (see also Mitchell, McNaughton, Flanagan, and Kirk (2008) for a review). Several studies have pointed out that FM-theta is generated in or near the anterior cingulate cortex (ACC) (Gevins, Smith, McEvoy, & Yu, 1997; Hanslmayr et al., 2008; Ishii et al., 1999; Onton, Delorme, & Makeig, 2005; Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007). With regard to WM increased FM-theta activity has mainly been observed in association with increase of task difficulty, memory load and sustained attention (Gevins & Smith, 2000; Gevins et al., 1997; Hanslmayr et al., 2008; Jensen & Tesche, 2002; Onton et al., 2005; Sauseng et al., 2007). However, its functional role in memory processes is still a matter of debate. Recently, it has been suggested that the "function" relying on FM-theta activity during WM task demands seems to be rather unspecific than reflecting a unitary cognitive (memory) process (Missonnier et al., 2006; Mitchell et al., 2008; Sauseng et al., 2007). For instance, it has been proposed that FM-theta elicited by WM tasks is more likely to reflect an attentional system which allocates and coordinates cognitive resources in order to solve the task (Missonnier et al., 2006; Sauseng et al., 2007). This interpretation is supported by the finding that the ACC, the generator of FM-theta, reflects monitoring processes and the recruitment of cognitive control (Badre & Wagner, 2004; Kerns et al., 2004). Moreover, it has been proposed that the ACC as well as several other prefrontal brain areas are part of a network of neuronal structures which represents central executive functions during WM demands. According to Baddeley (1996) the central executive represents an attentional control system that acts upon domain specific storage

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1074-7427/$ - see front matter
doi:10.1016/j.nlm.2009.09.013

components. This probably suggests FM-theta to be part of an attentional (executive) system based on prefrontal areas.

However, it would be a mistake to restrict a central executive system solely on prefrontal brains structures, as a large variety of executive processes can be ascribed to that system (Smith & Jonides, 1999). Indeed, several neuroimaging studies have provided evidence for the involvement of parietal brain areas in executive functions (Collette & Van Der Linden, 2002; Collette et al., 1999; Osaka et al., 2004). On the scalp level it has been shown that long-range connections between frontal and parietal areas in the theta frequency range are an indicator of executive processes during WM tasks (Sarnthein, Petsche, Rappelsberger, Shaw, & Von Stein, 1998; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005; Sauseng et al., 2006; Wu, Chen, Li, Han, & Zhang, 2007). For instance, Sauseng et al. (2005) reported an increase in fronto-parietal coupling in the theta frequency range during the manipulation of abstract visual patterns. In another study by Sauseng et al. (2007) it was shown that theta long-range coupling reflects specific integrative processes which are mediated by a central executive system, whereas fronto-central theta activity represents an attentional system indicative for allocating cognitive resources.

It is well known that WM *per se* incorporates a variety of distant brain areas. As theta oscillations in general are well suited to mediate long-range connections (Varela, Lachaux, Rodriguez, & Martinerie, 2001; Von Stein & Sarnthein, 2000) the question arises whether frontal theta activity is linked to more locally implemented networks located in other brain regions in order to allow for the coordination and integration of activity of those brain areas during WM. It has been shown that synchronous gamma oscillations are generated by local networks. Gamma oscillations (30–80 Hz) have also been considered to be involved in WM processes (Howard et al., 2003; Lutzenberger, Ripper, Busse, Birbaumer, & Kaiser, 2002; Mainy et al., 2007; Tallon-Baudry, Bertrand, & Fischer, 2001; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). It has been proposed that gamma oscillations are involved in mental representations and hence, seem to be a plausible candidate for the organization and maintenance of multiple items in WM. With regard to the many findings of theta and gamma oscillations in WM an interaction between theta and gamma oscillations during WM processes seems to be plausible. So far, only a few studies have tried to highlight the interrelation between theta and gamma oscillations during working memory demands (Canolty et al., 2006; Demiralp et al., 2007; Sauseng, Klimesch, Gruber, & Birbaumer, 2008; Schack, Vath, Petsche, Geissler, & Möller, 2002).

Therefore, the aim of the present study was to test whether FM-theta, which might be part of an attentional control system, is coupled to gamma, which reflects the temporal organization and segregation of items in WM, in a verbal delayed match to sample task. For this purpose we focused on EEG-power analyses (a measure for synchronous local activity) and cross-frequency phase synchronization (a measure for interactions between distant oscillatory brain activity at different frequencies) during the delay period of a verbal delayed match to sample task. The delayed match to sample task was characterized by a retention related condition and a manipulation related condition. The main difference between both conditions was that manipulation required higher demands on executive processes/top-down control, whereas pure retention involved less executive processes (see also Postle et al. (2006) for an extensive explanation). Specifically, we expected stronger FM-theta:gamma coupling in the manipulation compared to the retention condition as FM-theta is associated with attentional (executive) functions and gamma activity is associated with the sequential organization and temporal segregation of single items in WM.

2. Materials and methods

Thirty-one healthy volunteers participated in the experiment after giving written informed consent. Nineteen of thirty-one subjects were female with a mean age of 21.5 years (SD = 1.2) and twelve were male with a mean age of 23.9 years (SD = 3.8). All participants except for two were right-handed. fifteen subjects remained for data analysis as only those subjects were included who had more than 20 artefact-free trials remaining in each experimental condition (many participants tended to blink during the retention interval of the task, although instructed not to do so).

In the present study a verbal delayed match to sample task was performed. At the beginning of each trial three capital letters (only consonants) were presented in the centre of a computer monitor ($5.3^\circ \times 2.2^\circ$ visual angle; distance from monitor 130 cm) for 500 ms, either shown in red or in green. If the letters were shown in green (retention condition), subjects had to keep the sequence of letters in mind for 2500 ms. If the letters were shown in red (manipulation condition), subjects had to reorganize the letters in alphabetical order and maintain the new sequence for 2500 ms. After the delay period a probe (three capitalized letters) was presented for 1000 ms. Subjects had to decide by button press whether the retained or manipulated material was identical (match) to the probe stimulus or not (non-match). Inter-trial-interval was 3000 ms. A total of 80 trials was presented in randomized order (for each condition 40 trials). The proportion between match and non-match trials was 50% within each condition. In addition to the verbal delayed match to sample task participants had to perform a task switching experiment (Sauseng et al., 2006), a visuospatial working memory task (Sauseng et al., 2005) and a perceptual discrimination task (Hanslmayr et al., 2005).

EEG was recorded by a SynAmps amplifier (Neuroscan Inc.) from 19 Ag–AgCl ring-electrodes against a linked-earlobe reference. Electrodes were mounted according to the international 10–20 system on the following sites: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2. Signals were registered within a frequency range of 0.15–70 Hz and sampled with 500 Hz. A Notch-Filter was set at 50 Hz and impedance was kept below 8 kΩ. Two additional channels were used in order to control for vertical and horizontal eye movements. EOG correction (regression analysis as implemented in Neuroscan Edit 4.3) was applied and data were visually inspected for artefacts. Before data analysis sampling rate was changed from 500 to 512 Hz. For data analysis the first 2000 ms of the retention interval were taken into account. Data from every trial were segmented into four intervals of 500 ms which were then pooled together. This was done in order to increase the number of artefact-free trials. Any epoch of 500 ms that was artefact-free was included in further analyses. On average, we obtained 32 trials (first half of the delay period: 31 trials; second half of the delay period: 33 trials) for the manipulation condition and 32 trials (first half of the delay period: 33 trials; second half of the delay period: 33 trials) for the retention condition after artefact rejection. As performance was rather accurate, data from correct as well as incorrect responses were included in the analysis. For power analysis, data were first averaged over the 2000 ms delay period in order to see whether classical FM-theta activity is apparent. For the subsequent analyses (power as well as cross-frequency phase synchronization) the 2000 ms delay period was subdivided into two time intervals (time interval 1: 500–1500 ms, time interval 2: 1500–2500 ms) because we expected differences in the manipulation condition between the first and the second half of the delay period in such a manner that manipulation processes take place in the first half, whereas retention related processes take place in the second half of the delay period (see also Sauseng et al., 2005). For statistical analysis non-parametrical comparisons were performed because phase synchro-