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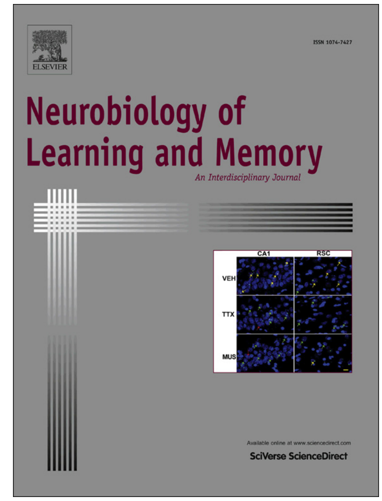

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Frontal midline theta connectivity is related to efficiency of WM maintenance and is affected by aging

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Abstract

Representations in working memory (WM) are temporary, but can be refreshed for longer periods of time through maintenance mechanisms, thereby establishing their availability for subsequent memory tests. Frontal brain regions supporting WM maintenance operations undergo anatomical and functional changes with advancing age, leading to age related decline of memory functions. The present study focused on age-related functional connectivity changes of the frontal midline (FM) cortex in the theta band (4-8 Hz), related to

WM maintenance. In the visual delayed-match-to-sample WM task young (18-26 years, N=20) and elderly (60-71 years N=16) adults had to memorize sample stimuli consisting of 3 or 5 items while 33 channel EEG recording was performed. The phase lag index was used to quantify connectivity strength between cortical regions. The low and high memory demanding WM maintenance periods were classified based on whether they were successfully maintained (remembered) or unsuccessfully maintained (unrecognized later). In the elderly reduced connectivity strength of FM brain region and decreased performance were observed. The connectivity strength between FM and posterior sensory cortices was shown to be sensitive to both increased memory demands and memory performance regardless of age. The coupling of frontal regions (midline and lateral) and FM-temporal cortices characterized successfully maintained trials and declined with advancing age. The findings provide evidence that a FM neural circuit of theta oscillations that serves a possible basis of active maintenance process is especially vulnerable to aging.

Keywords: working memory, functional connectivity, phase lag index, frontal midline theta, aging

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1. Introduction

Normal aging is associated with a decline in various memory and attentional abilities. This age-related memory impairment specifically involves the disturbed ability to encode new memories and dysfunction of working memory (WM) whereas implicit and autobiographical memory remains relatively intact. While the behavioral aspects of age-related decline in WM are well known , the changes of functional interactions between brain areas related to WM (especially during the maintenance period) across the lifespan are still largely unclear, and have not as yet been investigated by EEG studies. It is still a matter of debate which WM processes (encoding: Gazzaley et al., 2008; Karrasch et al., 2004, or maintenance: Cappell, Gmeindl, & Reuter-Lorenz, 2010) underlie much of the WM deficits observed in the elderly. We aimed to test the frontal lobe theory of age-related WM decline during the maintenance period of a delayed match to sample task. The goal of the current study was to investigate the age related functional connectivity (FC) correlates of WM maintenance processes, mediated by phase synchronization of frontal midline (FM) theta oscillations.

WM is a limited capacity neurocognitive system which serves the temporary maintenance of the required information to achieve future goals (Baddeley, 2003). By these means learning to utilize information beyond its transient sensory availability can be realized. Maintenance mechanisms refer to the repetitive selection or direction of attention to the relevant representations (D'Esposito, 2007). Thus, forgetting occurs when items fail to compete with other ones to regain the limited focus of attention (interference), or when the representation declines over time (decay) (Jonides et al., 2008).

In EEG studies sustained increased power of theta oscillations (4–7 Hz) was consistently observed particularly within the FM regions during the maintenance of information in WM paradigms (for review see Klimesch et al., 2008; Mitchell et al., 2008). Corresponding to the relationship between FM theta oscillations and the maintenance mechanism it was demonstrated that when theta activity during retention was reduced, performance decreased

(Klimesch et al., 2006). In association with an increasing number of items held in WM FM theta amplitude was shown to be enhanced (for example Onton et al., 2005; Jensen and Tesche, 2002; Missonnier et al., 2007) which was found most consistently during the retention interval regardless of the type of information (verbal, visuospatial). Therefore, it was suggested that the observed FM theta activity could reflect top-down modulation which helps to maintain the activation of cortical representations of the object after it is no longer present (for review see Mitchell et al., 2008).

Interactions among brain areas related to memory functions can be particularly important with respect to the fronto-cortical top-down control mechanisms that serve memory processes (Stam et al 2012). FC behind EEG oscillations can be assessed by measuring the phase synchronization of EEG-signals between pairs of electrodes (Varela, Lachaux, Rodriguez, & Martinerie, 2001). By establishing sustained coordinated timing of neuronal firing between distant cortical areas oscillatory synchronization integrates anatomically distributed processing and facilitates neuronal communication, thus for instance has a central role in input selection and synaptic plasticity (Fell & Axmacher, 2011). Maintenance of visual information in WM enhances theta-synchrony between frontal and temporo–parietal as well as between occipito-temporal regions (Sarnthein et al., 1998; Sederberg et al., 2003; Sauseng et al., 2005; for review see Klimesch et al., 2008). Decreased interactions between fronto-temporo-parietal networks was found during resting state and perception (Sarnthein et al., 1998) compared during WM tasks. Increasing the number of items to be retained was found to be associated with increased theta connectivity between frontal and temporo–parietal regions (Sauseng and Klimesch, 2008; Sauseng et al., 2005) and between temporo-occipital regions during the delay-period (for review see Klimesch et al., 2008). For example, the level of theta connectivity within the fronto-temporo-parietal network predicts individual working memory capacity (Kopp et al., 2006 for review Payne and Kounios, 2009). It was discussed by Sauseng et al. (for review Sauseng et al., 2010) that connectivity within the fronto-parietal network established by theta oscillations might be associated with the control of the frontal cortex on the activation level of higher-order sensory areas (posterior association cortex, where sensory information is thought to be stored).

Recent fMRI analysis of FC revealed that the interruption of the maintenance mechanism by distractor stimuli results in the disruption of connectivity between the frontal and sensory cortices (Clapp & Gazzaley, 2012). Therefore, it was assumed that frontal regions are likely to be involved in processes related to attention that optimize memory formation by selecting and continuously updating the relevant representations (Curtis & D'Esposito, 2003). In addition, increased fronto-temporal phase synchronization together with synchronization within the medial temporal lobe (between the rhinal cortex and the hippocampus) were suggested to be the neural signature of long-term memory formation, corresponding to the idea that phase synchronization facilitates neural plasticity (for review see Fell and Axmacher, 2011).

According to the frontal lobe theory of aging many age-related changes in cognition are due to vulnerability of the frontal lobes where substantial neuroanatomical and neurochemical changes occur with advancing age (Raz and Rodrigue, 2006 for review). fMRI studies found reduced activation in older compared to young adults in brain areas supporting memory function, such as the frontal cortex and the medial-temporal lobes (Grady et al., 2003; Johnson et al., 2004). For instance, age-related deficits in prefrontal cortex activation were shown to have a great impact on tasks which were dependent on executive functions (West, 1999; Cabeza, 2004 for reviews). With healthy aging, delta (0.5-4 Hz) and theta activity diminishes, and fast frequencies (beta:13-30 Hz and gamma:40-70 Hz) are enhanced (Werkle-Bergner et al., 2006; Cummins et al., 2008). Karrasch et al., reported that older adults showed less theta event related synchronization during the encoding period in a Sternberg memory task (Karrasch, Laine, Rapinoja, & Krause, 2004). Cerebral aging clearly has an effect on the dynamics of theta oscillations and thereby is likely to impair either memory storage or sustained attention processes, or both, during maintenance of information, and consequently is assumed to lead to decreased performance in the elderly.

Since the coupling of the FM theta oscillation is known to be an essential neuronal signature for WM maintenance we hypothesize that the network of FM theta activity may be affected by normal aging not only during information encoding but also during the period of retention. Therefore, changes of the FM theta network characterizing WM retention could be linked to the decline of memory functions in the elderly. The present study aimed to test whether 1) FM theta connectivity during retention period was related to the efficiency of WM maintenance in addition to the actual capacity of WM 2) FM theta connectivity during retention period declined in older adults, and 3) impaired WM maintenance mechanisms underlie the behavioral WM deficits observed in the elderly. In the visual delayed match to sample task young and elderly subjects had to memorize sample stimuli consisting of 3 or 5 items. Such a type of WM task allows the investigation of maintenance without perceptual processes, as well as the study of the variation of the task demand from one trial to the other. Besides the memory task a control task (visual odd-ball task) was also introduced. Both the control and memory tasks consisted of the same set of visual stimuli and temporal design of the presentation. The control task used in the present study (in contrast to the often used resting state condition in EEG studies of memory) obviously induces sustained attentional state just as like memory task do as well(especially during the maintenance of perceived information in the absence of the sensory input). The contrasting of the memory and control tasks therefore permits the dissociation between physiological measures of memory maintenance and that of sustained attentional functions. We assume that the FM-theta FC is diminished in the elderly only in the memory task which may account for the WM decline in aging.

The FC between regions represented by EEG channels was determined by the computation of the phase lag index (PLI) (Stam et al., 2007). For EEG analysis, the low and high memory demanding maintenance periods were classified based on whether the trials were remembered (termed as successfully maintained) or later unrecognized (termed as unsuccessfully maintained). Previous EEG studies investigating oscillatory characteristics of memory maintenance in retention period only focused on the effects of memory load (Hsieh & Ranganath, 2013 for review). We extended the analysis of maintenance processes and compared EEG characteristics of EEG epochs corresponding to successfully versus unsuccessfully maintained items which may reveal additional FC-s beyond those that are sensitive to increasing memory load. Differences in the strength of connectivity resulting from the comparison of the successfully versus unsuccessfully maintained items was thought to characterize the pattern of neuronal network during the time of retention, that may considered to be a predictive indicator of successful maintenance processes (Paller and Wagner, 2002). The comparison of low and high memory demanding trials aimed to reveal sustained functional network of FM theta related to the capacity of WM. It is expected that the characteristics of these two functional networks corresponding to successful memory maintenance and/or memory capacity may not entirely overlap and thus its investigation may reveal so far unknown vulnerable FC characteristics related to aging.

2. Methods

2.1 Subjects

20 young (18-28 years; male/female ratio: 5/15; mean age: 21.1±5.6), and 16 elderly (61-71 years; male/female ratio: 3/13; mean age: 65.8 ±3.16) adults participated in the study. All of them were right handed and had normal or corrected vision. The participants signed an informed consent about the study and received financial compensation for participation. The study was approved by the relevant institutional ethics committee. The two groups were matched with respect to sex and years of education (young mean years: 12.6±1.9; elderly mean years: 13.5±2.9; no significant difference between groups was found regarding to the mean years of education). The IQ of all participants was measured by Wechsler Adults Intelligence Scale-WAIS which revealed no significant group differences (young IQ=117.6 ±7.1; Performance IQ=125.9±8.6; Verbal IQ=118.3±8.7; elderly IQ=117.3 ±9.2; PQ=118 ±11.5; VQ=115.6 ±8.6).

2.2 Stimuli

Stimuli were presented against a black background on a 19" CRT computer monitor at a viewing distance of approximately 125 cm. An array of 3 or 5 colored squares was used as study and test stimuli in distinct locations of the black display (each square with 6.5 cm height and 6.5 cm width). The 3 or 5 colors of the squares which form an array were selected from possible 8 highly-discriminable colors. A given color appeared only once within a sample and test array. The following colors were used: red (RGB: 255, 0, 0), yellow (RGB: 255, 255, 0), gray (RGB: 139, 139, 139), green (RGB: 0, 255, 0), brown (RGB: 210, 105, 30), cyan (RGB: 0, 255, 255), pink (RGB: 255, 105, 180), blue (RGB: 255, 255, 255), white (RGB: 255, 255, 255), and violet (RGB: 160, 32, 240). The locations of the squares were defined by segmenting the display into a 7×7 matrix which yielded 49 possible locations of one square.

2.3 Memory task and procedure

The task used in the present study was a modified version of a WM task previously used by Vogel and Machizawa, 2004. Subjects performed a visual delayed match to sample task, in which they were instructed to memorize the colors of the sample array (distinctly colored squares). Following a delay period the participants were instructed to recognize the currently seen array by matching the sample to the test array. The test array was either identical to the sample array or differed only by one color. The locations in which the colored squares were presented did not change in the test array compared to the locations in a previous study array. Depending on the task demands 3 or 5 locations were selected randomly from the 49 possible locations. The color of one square in the test array was different from the corresponding item in the sample array in 50% of trials. Two memory load conditions were used: in the low memory load condition an array consisted of 3 squares whereas in the high memory load condition an array consisted of 5 squares. Subjects pressed one of two buttons by using two hands to indicate whether the two arrays were identical or different.

The subjects performed a total of 192 experimental trials distributed in 6 blocks (32 trials in each block). Within each block in a counterbalanced (50-50%) and randomized way trials from both low and high memory load conditions were presented. In an experimental trial (Figure 1) first a blank screen with a fixation cross located in the center of the screen was shown for 300 ms which was followed by the presentation of the sample array (duration: 1500 ms). A blank screen with a fixation cross was present for a 4100 ms long delay interval (retention). Following the offset of the retention period the test array appeared until the subject made a same (match) or different (mismatch) response within a 4000 ms time window by using a game pad (right for match and left for mismatch response). Subjects were asked to respond as quickly and as correctly as possible. At the end of each trial feedback on correct/incorrect responses was given on the display.

2.4 Control task

A visual odd-ball task was performed by the participants as a control task before the memory task. Both the control and memory tasks consisted of the same set of visual stimuli and temporal design of stimulus presentation. In contrast to the memory task in the control task the participants were asked to indicate the appearance of a red square within the array of 3 or 5 squares by button press. The target item (red square) occurred in 32% of the trials). Only the non-target trials were included in the data analysis. The participants performed one block of 50 trials. The stimuli with 3 or 5 items were presented during the trials in counterbalanced and randomized way. The control task required perceptual discrimination; therefore identically to the memory task sustained attentional state was needed to accomplish it, without any demand of memory maintenance.

-- Figure1. ---

2.5 EEG data collection

The data was recorded in an acoustically attenuated and electrically shielded chamber. The participants were seated in front of a 19 inch CRT computer screen (125 cm distance). The

Neuroscan software and Nuamps amplifiers were used for 33 channel EEG recording (Ag/AgCl electrodes placed according to the international 10-20 system). The impedance of the electrodes was kept below 10 kΩ. Vertical (from above and below the left eye) and horizontal (from left and right outer canthi) eye movements were recorded. The reference electrode was placed on the tip of the nose and an electrode placed between Cz and Fz was used as ground. The sampling rate was 1000 Hz and signals were on-line filtered with a 70 Hz low-pass digital filter.

2.6 Data analysis

Performance was evaluated in terms of accuracy which was measured as the percentage of correct responses for the test arrays relative to all the trials presented. Correct responses corresponded to correct change detection, and correct rejection if there was no change in the stimuli. Accuracy was calculated separately for conditions of low and high task demands. For recognition speed (reaction time) data was calculated for each condition by including only reaction time of the correct responses. The WM capacity of the participants was tested before the EEG recording with the digit span task included in the WAIS. The overall digit span score, and the scores for the forward and backward task parts were used to further test the between group differences in WM capacity.

The EEG recorded during the memory maintenance corresponding to the delay period was selected for analysis, thus visual evoked potentials elicited by previously presented stimuli had no effect on the analyzed data. From the control task EEG epochs recorded in the delay period were analyzed regardless of the sample size. To avoid the movement artifacts elicited by the button press target trials were excluded from the data analysis. The EEG was filtered (24 dB/octave rolloff) in the theta (4-8 Hz) frequency band. The entire interval of the retention period was analyzed by extracting two 2048 ms long EEG epochs from the 4100 ms retention period. This procedure resulted in an increased number of artifact free epochs which were averaged for the final analyses. Independent Component Analysis (Matlab 2009b software; EEGLab 10.2.5.8b toolbox; ADJUST version 3 plugin) and visual screening were applied for artifact (blinking, movement, etc.) removal. ADJUST plugin based on stereotyped spatial and temporal features as artifacts can detect automatically Independent Components of artifacts (optimized to capture blinks, eye movements and generic discontinuities). These artifacts can be removed from the data without affecting the activity of neural sources (Mognon et al., 2010).

EEG epochs of the memory task were analyzed separately for low and high memory load trials according to later recognition performance. As a result the successfully and unsuccessfully maintained trials of the retention period were distinguished in both the low and high memory load conditions. This procedure resulted in 4 trial categories: successfully maintained and unsuccessfully maintained trials both in the low and high memory load conditions. The relatively high performance in the low memory condition resulted only in a few unsuccessfully maintained trials which were therefore excluded from the further analysis. In order to counterbalance the difference between any conditions with respect to the number of epochs the same number of epochs/subject was selected in randomized manner from each condition. As a result 86 epochs/ subject were selected to the compare control and memory task respectively. 81 epochs/ subject were selected to the compare low and high condition, respectively. 56 epochs/ subject were selected to the compare successfully and unsuccessfully maintained trials respectively.

The strength of FC was calculated by measuring multichannel phase synchronization with using the Brainwave software (0.9.38 version; http://home.kpn.nl/stam7883/brainwave.html). The level of FC between any two channels i and j is defined as the phase lag synchronization (phase lag index: PLI). PLI measures the asymmetry of the phase difference distribution between two EEG signals, and reflects the consistency with which one signal is phase leading or phase lagging with respect to another signal (a detailed mathematical description can be found in Stam et al., 2007). PLI was shown to be sensitive in detecting dynamical changes of phase relationship between brain regions and also efficient to eliminate the effect of volume conduction (effect of common sources on the EEG signal) and independent of the reference electrode. Random phase differences indicating low connectivity strength are expressed as PLIs values around 0 whereas high connectivity strength results in PLIs values around 1. The FC between all pairs of electrodes obtained in all the EEG epochs was averaged across conditions respectively. The region of FM area was defined corresponding to electrodes Fp1, Fp2, Fz, FC1 and FC2. The average PLI for all channels within the FM region (local - intra-regional synchronization) was assessed for all conditions separately. Long distance (inter-regional) synchronization for the FM area was calculated for the left and right FM -temporal, FM-parietal, FM-occipital regions and FM -lateral frontal regions for all conditions, respectively. For this analysis the rest of the EEG channels were grouped into eight regions of interest (ROIs): lateral frontal (left: F3, F7, FC5; right: F4, F8, FC6); temporal (left: FT9, T7, TP9; right: T8, FT10, TP10), parietal (left: CP1, CP5, P7, P3; right: CP2, CP6, P8, P4) and occipital (left: PO9, O1; right: PO10, O2). The average PLIs between the FM region and all other ROIs were calculated.

Statistical analysis was performed with the Statistica software (version 11.0). **1)** For the behavioral data, two-way ANOVAs were performed on reaction time, and accuracy data in a group × memory load condition design. One-way ANOVAs were performed on the digit span task scores, in which the group was used as the between subject factor. **2)** For statistical analysis of difference between control and memory task for FM connectivity mixed model ANOVAs were performed for each ROIs separately involving age group as between subject factor and task type as within subject factor. **3)** Memory performance effect on FM connectivity was tested using successfully and unsuccessfully maintained trials in the high memory load condition. For each ROIs separately mixed model ANOVA was performed involving age group as between subject factor and trial type as within subject factor. **4)** The analysis of memory load effects involved the correct trials in the low and high memory load conditions (mixed model ANOVA was applied for all 9 ROIs separately using memory load as within subject factor and group as between subject factor). **5)** For the study of the relationship between individual FM connectivity and memory performance Pearson correlation analysis was conducted between accuracy and the PLI of ROIs separately. EEG data for this analysis involved the correct trials in the high memory load. For post hoc analysis the Tukey test was used.

3 Results

3.1 Memory performance: accuracy, reaction time, IQ measures

Overall both the young and elderly adults performed well above chance level on the memory task. Details are shown in Table 1. According to the significant main effect of age ($F_{1, 34}$= 29.6, p <0.001 partial eta square η2=0.44) the performance of elderly was lower than that of the young adults. The observed main effect of memory load ($F_{1, 34}$= 174.2, p <0.001; η2=0.85) indicated that the performance decreased as a function of increasing memory load. Significant age and memory load interaction effect was also found ($F_{1, 34}$= 4.4, p=0.044; η2=0.12). According to the post hoc tests the decrease of accuracy as a function of memory load was evident in both groups (post hoc, p<0.001), and the effect of age in the high memory load condition was more conspicuous than in the low memory load condition (post hoc, p=0.001 at the low, and p<0.001 in the high memory load trials. There was no age group difference related to reaction time. On the contrary, a slowing of reaction time was observed in the high compared to that seen in the low memory load condition which was indicated by the significant main effect of memory load ($F_{1, 34}$= 36.15, p<0.001; η2=0.46). Analysis of the digit span performance revealed significant main age effect [$F_{1, 34}$=13.08; p<0.001; η2=0.28], indicating higher WM capacity in the young compared to the elderly adults (see Table 2.). The analysis of task subsets (backward and forward digit span) indicated the effect of age with respect to the forward digit span performance which was marginally significant ($F_{1, 34}$=3.89; p=0.057; η2=0.1), while it was clearly evident in backward digit span performance ($F_{1, 34}$=11.58; p=0.002; η2=0.25).

--- Table1. ---

--- Table2. ---

3.2 Control and memory task differences on FM connectivity (PLI)

PLI within the MF region: Significant task type and age interaction effect ($F_{1,\ 34}$=9.78, p=0.004; η2= 0.22) was observed. The connectivity within MF ROI was found to be decreased in the elderly compared to the young only during the memory task (p<0.001) but not in the control task. The pairwise contrast analysis of the control and the memory task in each group revealed increase of PLI within the MF cortex only in young (p=0.002), but not in the elderly. In conclusion the source of interaction is that the age related differences were absent in the control task and were evident only during the delay period of the memory task. A significant decrease of PLI within MF region was also evident in the elderly (main effect of age - $F_{1,\ 34}$=11.62, p=0.002; η2=0.25).

PLI between the MF and left lateral frontal ROIs: significant task type and age interaction effect ($F_{1,\ 34}$=9.63, p=0.004; η2=0.22) was observed. The connectivity was found to be decreased in the elderly compared to the young only during the memory task (p<0.001). The pairwise contrast of the control and memory tasks revealed a significant increase of PLI between ROIs (p<0.001) only in the young. Significant main effect of age (decrease of PLI between ROIs in the elderly; main effect of age - $F_{1,\ 34}$=11.01, p=0.002; η2=0.24) and main effect of task type (increased PLI between ROIs in memory task $F_{1,\ 34}$=4.41, p=0.043; η2=0.12) were also obvious.

PLI between the MF and right lateral frontal ROIs: Significant task type and age interaction effect was observed ($F_{1,\ 34}$=8.56, p=0.006; η2=0.20). During the memory task decreased connectivity was found in the elderly compared to the young (p=0.019). The contrast analysis of the control and memory tasks revealed a significant increase of PLI between ROIs only in the young (p<0.001). Significant main effect of age (decrease of PLI between ROIs in elderly; $F_{1,\ 34}$=7.91, p=0.008; η2=0.18) was found.

PLI between the MF and left temporal ROIs: significant task type and age interaction ($F_{1, 34}$=6.76, p=0.014; η2=0.16) was observed. Connectivity was decreased in elderly compared to young (p<0.001) only during the memory task., Significant increase of PLI between ROIs was observed between the control and memory task (p=0.049) only in the young. Decrease of PLI between ROIs in the elderly was revealed by the significant main effect of age ($F_{1, 34}$=6.73, p=0.014; η2=0.16; η2=0.16).

PLI between the MF and right temporal ROIs: significant task type and age interaction ($F_{1, 34}$=13.17, p=0.001; η2=0.27) was found. Connectivity was found to be lower in the elderly compared to the young only during the memory task (p<0.001). The contrast of control and memory task in each group revealed that while in the young connectivity between ROIs tended to increase in the memory task (p=0.091), in the elderly PLI between ROIs was observed to be significantly decreased (p=0.002). Significant main effect of age (decrease of PLI between ROIs in elderly; $F_{1, 34}$=10.08, p=0.003; η2=0.23) was found.

PLI between MF and left and right parietal ROIs: Main effect of age was observed between the MF and left parietal ($F_{1, 34}$=9.46, p=0.004 η2=0.22) and and right parietal ROI ($F_{1, 34}$=5.97, p=0.02; η2=0.14). In contrast to the young a generally lower level of connectivity between these ROIs characterized the elderly.

PLI between MF and left occipital ROIs: A significant interaction of task type and age was seen ($F_{1, 34}$=6.07, p=0.019; η2=0.15). Pairwise contrast of age group differences in each task type revealed decreased PLI between ROIs in the elderly (p<0.001). By comparing memory and control task differences in the group of elderly, PLI between these ROIs was found to be significantly decreased in memory task (p=0.025). PLI was found to be different between groups: a substantial decrease was observed in the elderly compared to the young (age main effect -$F_{1, 34}$=9.85, p=0.004; η2=0.22).

PLI between MF and right occipital ROIs: Interaction of task type and age was found to be significant ($F_{1, 34}$=6.46, p=0.016; η2=0.16). Decreased PLI was observed between ROIs in the elderly compared to young but only during the memory task (p=0.002). Decreased PLI was found between these ROIs during memory task compared to control only in the elderly (p=0.013). PLI was found to be decreased in the elderly compared to the young (age main effect - $F_{1, 34}$=4.63, p=0.039; η2=0.12)

--- Figure2. ---

3.3. Successfully and unsuccessfully maintained trials differences in strength of phase synchronization

PLI within the MF region: Significant decrease of PLI within the MF region was obvious in the elderly compared to the young (main effect of age -$F_{1, 34}$=31.52, p<0.001; η2= 0.48). The connectivity within MF was found to be decreased in unsuccessful compared to successfully maintained trials (main effect of trial type -$F_{1, 34}$=7.01, p=0.012; η2=0.17)

PLI between the MF and left lateral frontal ROIs: Significant task type and age interaction ($F_{1, 34}$=5.29, p=0.028; η2=0.13) was observed. By comparing trial type differences in each group, a significantly higher PLI was found in successfully maintained to trials relative to unsuccessful ones only in the young group (p=0.008). The connectivity between ROIs was found to be generally decreased in unsuccessful compared successfully maintained to trials (main effect of trial type -$F_{1, 34}$=5.33, p=0.027; η2=0.14). Significant main effect of age (decrease of PLI between ROIs in elderly; $F_{1, 34}$=20.63, p<0.001; η2=0.37) was found.

PLI between the MF and right lateral frontal ROIs: Significant decrease of PLI was observed in the elderly compared to the young (main effect of age -$F_{1, 34}$=14.16, p<0.001; η2=0.29). The connectivity between ROIs was found to be decreased in unsuccessful compared to successfully maintained trials (main effect of trial type - $F_{1, 34}$=5.54, p=0.025; η2=0.14)

PLI between the MF and left temporal ROIs: Significant task type and age interaction ($F_{1, 34}$=4.18, p=0.049; η2=0.11) was observed. By comparing trial type differences in each group, a significantly higher PLI was found in successfully maintained trials relative to unsuccessful ones only in the young group (p=0.041). The connectivity was decreased in elderly compared to young (p<0.001) only during successful trials. According to the observed main effect of age substantially decreased PLI was evident in the elderly relative to the young group $F_{1, 34}=11.31$, p=0.002; η2=0.02).

PLI between the MF and right temporal ROIs: Significant decrease of PLI was observed in the elderly compared to the young (main effect of age - $F_{1, 34}=17.25$, p<0.001; η2=0.33). The connectivity between ROIs found to be decreased in unsuccessful compared to successfully maintained trials (main effect of trial type -$F_{1, 34}=6.34$, p=0.017, p=; η2=0.16).

PLI between MF and left and right parietal ROIs: Main effect of age was observed between MF and left parietal ROI ($F_{1, 34}=11.94$, p=0.002; η2=0.26) and also between the MF and right parietal ROI ($F_{1, 34}=11.767$, p=0.002; η2=0.26). In contrast to the young a generally lower level of connectivity between ROIs characterized the elderly.

PLI between MF and left occipital ROIs: A significant decrease of PLI was observed in the elderly compared to the young (main effect of age -$F_{1, 34}=15.09$, p<0.001; η2=0.3). The connectivity between ROIs was found to be decreased in unsuccessful compared to successful trials (main effect of trial type $F_{1, 34}=9.47$, p=0.004; η2=0.21).

PLI between MF and right occipital ROIs: Significant decrease of PLI was observed in the elderly compared to the young (main effect of age -$F_{1, 34}=13.87$, p=0.001; η2=0.29). The connectivity between ROIs found to be decreased in unsuccessful compared to successful trials (main effect of trial type $F_{1, 34}=7.81$, p=0.009; η2=0.19).

---Figure 3. ---

3.4. Memory load effect on strength of phase synchronization

PLI within the MF region: In the elderly relative to the young decreased PLI was observed (age main effect $F_{1, 34}=15.73$, p<0.001, η2=0.32).

PLI between the MF and left and right lateral frontal ROIs: In the elderly compared to the young a general decrease of PLI was observed in the left (age main effect $F_{1,\ 34}$=14.11, p<0.001 η2=0.29) and also between the ROIs in the right side ($F_{1,\ 34}$=17.89, p<0.001; η2=0.34).

PLI between the MF and left and right temporal ROIs: In the elderly compared to the young a general decrease of PLI was observed (age main effect, left: $F_{1,\ 34}$=5.73, p=0.022; η2=0.14 and right: $F_{1,\ 34}$=23.08, p<0.001; η2=0.4)

PLI between MF and left parietal ROIs: In the elderly compared to the young a general decrease of PLI was observed between ROIs in the left side (age main effect $F_{1,\ 34}$=5.44, p=0.026; η2=0.14).). A tendency was observed regarding to the connectivity between ROIs indicating increased in the high compared to the low memory load condition (main effect of memory load - $F_{1,\ 34}$=3.42, p=0.073; η2=0.09).

PLI between MF and right parietal ROIs: In the elderly relative to the young decreased PLI was observed (age main effect $F_{1,\ 34}$=8.88, p=0.005; η2=0.21). A tendency was observed regarding to the connectivity between ROIs indicating increased in the high compared to the low memory load condition ($F_{1,\ 34}$=6.89, p=0.013; η2=0.17).

PLI between MF and left occipital ROIs: In the elderly relative to the young decreased PLI was observed ($F_{1,\ 34}$= 13.51, p<0.001; η2=0.28). Significant task type and age interaction effect ($F_{1,\ 34}$= 5.70, p=0.023; η2=0.14) was observed. By comparing load condition differences in each group, a tendency of higher PLI was found in the high load condition compared to low memory load only in the young group (p=0.082). Age related difference was only significant (p=0.003). at high memory load condition

PLI between MF and right occipital ROIs: In the elderly compared to the young decreased PLI was observed ($F_{1,\ 34}$=19.92, p<0.001; η2=0.36). A marginally significant memory load condition main effect was observed ($F_{1,\ 34}$= 3.93, p=0.056 η2=0.10) indicating that an increased PLI characterized the high compared to the low memory load trials.

--Figure 4. --

3.5 Relationship between theta FC and memory performance

Significant positive correlations were observed between the individual connectivity within and between ROIs and memory performance. The strength of FM theta FC during the retention period statistically predicted (with 13-34 % accuracy, see detailed r^2 indices in Table 3.) the latter memory performance. Significant positive correlations were also observed between the individual connectivity strengths between ROIs (MF-parietal and MF- occipital ROIs) and the digit span task performance (see Table 3.).

-- Table3. --

4 Discussion

The present study for the first time shows that connectivity patterns of the FM theta frequency band activity is directly related to efficiency of WM maintenance and is affected by aging. Functional interactions of the MF cortex were proved to be facilitated during the retention period of the WM task relative to the visual oddball control task. Age related deficits of FM connectivity were linked to the memory maintenance processes. It was also demonstrated that interactions of the FM cortex facilitates latter recognition memory. The stronger the functional interactions of FM theta activity were that characterized the retention of an item, the better was its later recognition. In the elderly substantially reduced connectivity strength of the FM region in association with decreased performance was evident suggesting that impaired maintenance processes mediated by FM theta phase synchronization plays a role in the WM deficits observed in elderly.

4.1 Working memory decline in association with aging

In line with the widely demonstrated WM decline related to aging, substantial WM impairment with advancing age was evident, but only for recognition accuracy and not for reaction time data. Also the increasing amount of information to be held in WM disrupted the efficiency of memory performance and slowed down the recognition process. As the function of higher memory load the age related differences became more apparent, which confirms the well-established age-related diminished processing resources (reduced attentional capacity or cognitive slowing) during WM task (West, 1999). The cognitive slowing theory of aging argues that there is more time for WM contents to decay due to slower processing in the elderly, which leads to reduced capacity. However, the decline of WM capacity cannot be only attributed to slowing because WM capacity declines more in the elderly than response speed, as it was confirmed by the present data. Van der Linden (1994) suggests that attentional resources linked to FM cortex undergo a marked decline with ageing whereas the storage capacity remains relatively unaffected (as described by the frontal lobe theory of aging). Accordingly, WM capacity measured by digit span task confirmed that the component of WM capacity depending on executive processes (indexed by the backward subtest) is more likely to account for age related deficits of WM than the storage capacity (indexed by the forward subtest).

4.2 The potential role of FM theta FC during maintenance in WM

The contrast of WM and control visual oddball tasks permitted the assessment of the differences between FM theta functional connectivity characteristics of memory maintenance and sustained attentional functions. Substantially increased connectivity strength within the FM cortex and between the FM and lateral frontal and temporal regions were observed during the retention period of the WM task compared to that seen in the control periods. In contrary the interactions between MF and the parietal and the occipital cortices were involved to the same extent during oddball as in WM tasks. FM theta oscillations have been widely documented to be involved not just in memory functions but also in a wide range of attention demanding tasks (for review see: Mitchell et al., 2008, Onton et al., 2005). As a potential generator of FM theta activity the anterior cingulate cortex and medial prefrontal cortex were implicated independently of the hippocampal system (Pizzagalli, 2006; Hsieh & Ranganath, 2013 for review). Up till know electrophysiological studies compared only resting state with memory retention period characteristics. According to these results decreased interactions between the entire fronto-temporo-parietal networks were found during the resting state compared to WM tasks (Sarnthein et al., 1998; Sederberg et al., 2003; Sauseng et al., 2005; for review see Klimesch et al., 2008). Contrary to the above, the present results indicate that maintenance of visual information in WM enhances theta-synchrony within the frontal and between the fronto-temporal cortices while attentional functions required by both WM and oddball tasks may be supported by the same fronto parieto-occipital theta phase synchrony. Verification of this hypothesis also comes from the correlations observed between FM theta connectivity and behavioral indices. Individual WM capacity was found to be correlated exclusively with fronto-parietal connectivity strength, while the success of performance in the recognition memory task was predicted by the functional links of FM brain site and all other brain regions.

Although the evidence relating WM processes to FM theta activity is quite clear as found in the present study and in others (Sauseng and Klimesch, 2008) there is still no conclusive interpretation regarding its functional significance. One of the putative hypotheses suggests that theta oscillation might coordinate the activation of relevant object information maintained in more posterior brain regions during WM (Sauseng, 2005), whereas the other assumes that theta activity regulates the activation of different items such that each item representation is sequentially activated at different phase of the theta cycle based on the temporal order in which it is perceived (Raghavachari et al., 2006). A possible function of theta oscillation is to hold memory representations in an active state by providing a sustained neural activation that can bridge the temporal gap of the delay period between stimulus presentation and memory test (McClelland et al., 1995). However, it is well-established that the amplitude of this oscillation decreases over time in the lack of regular refreshment (Sauseng and Klimesch, 2008). Our results may indicate that the functional connections of FM theta could serve a top-down function of the FM cortex by influencing the dynamical theta activity of brain regions which maintain only relevant object features (visual, etc.). This hypothesis suggests that the content of WM will decay if FM theta connectivity fails to reach an optimal level for its updating.

4.3 Functional connections of FM region during maintenance period modulated by WM load

Increased interaction was shown in the theta band functional network between FM and visual cortices (occipital regions) and also between FM sites and higher-order sensory areas of the parietal region as an effect of increasing memory load. This modulation of FM connectivity strength with memory load replicates the results of previous studies (Sauseng et al., 2005) showing the coupling of frontal and sensory areas during the performance in a WM task. This mechanism implies that the theta activity modulated by the FM area might enhance neural representations of relevant sensory stimuli by controlling when and which representations are reactivated in the sensory cortices thereby making information available for recognition. The above mechanism is supported by models suggesting that the top-down signals from the frontal cortex select and reactivate temporarily stored representations thus enhancing the rehearsal of those items (Curtis & D'Esposito, 2003).

4.4 Functional connections of FM theta during WM maintenance is predictive for subsequent memory

The EEG FC characteristics of the retention period in relation to later memory performance have not yet been investigated. According to our results within and between frontal cortices, FM-temporal and FM-occipital interactions were substantially facilitated during the successfully maintained, i.e. later correctly recognized trials. Only one study (Fernandez et al., 2000) investigated the changes of the theta rhythm in relation to correct and incorrect responses during the delay period of a verbal Sternberg task. Prior to correct responses a significant increase in the theta band power was observed. The present data support earlier findings that theta activity in the delay period is predictive for the efficiency of memory performance. According to our findings, the coupling within the regions of frontal cortex and fronto-temporal sites were not found to be sensitive for the modulation of memory load, but were predictive for the efficiency of maintenance processes. Therefore, it appears that fronto-parietal connectivity corresponds to the amount of information to be held in WM even if item recognition fails. This result indicates that the process of effective active maintenance is at least distinguishable from the actual capacity of WM retention. Further studies are needed for the conclusive interpretation of the significance of these functional interactions. However, based on the FM theta connectivity characteristics observed during memory processes some possible inferences can be proposed. Available evidence from EEG and fMRI data suggest that successful encoding into LTM depends on close interactions between frontal and temporal regions. Stronger activation of these regions positively correlates with performance on a later memory test (see Paller and Wagner, 2002; Fell and Axmacher, 2011 for a review). Theta rhythm resulting from hippocampal-cortical interactions proved to be important for encoding episodic memories via long-term potentiation and depression (i.e. Kahana et al., 2001). Furthermore, Jonides argued that the same neural representations initially activated during the encoding of information show sustained activation during retention or retrieval from LTM into WM (Jonides et al., 2008). Therefore, a possible assumption could be that the retention interval of the present task enables also consolidation processes into LTM. Several fMRI studies have shown that the role of the medial temporal region is important when retention intervals are longer than a few seconds (Cabeza, Ciaramelli, Olson, & Moscovitch, 2009). It is also possible that functional interactions of frontal cortex during maintenance may involve retrieving long-term representations associated to the sensory stimuli.

4.5 Age related alterations of FM theta connectivity during the WM retention

The present study provides further evidence for altered FC of the FM theta network in the elderly. In line with our hypothesis particularly in WM task FM-theta FC (within the MF and between MF-lateral frontal and MF-temporal regions) were observed to decline in the elderly. These age-related differences were found to be absent in the control task and were only evident during the delay period of the WM task indicating that active memory maintenance is specifically affected by advancing age. This decline of FC specifically seen during WM maintenance related to advancing age (indicated by partial eta squared scores of age main effects of each ROIs) was observed to be more apparent in the anterior than the posterior brain regions. The age related differences of slow oscillatory activities might be attributed to the general effect that with healthy aging peak frequencies of delta and theta bands may change (Werkle-Bergner et al., 2006). However, in the present results showing WM maintenance specific decline of FC with advancing age, not seen during the oddball task rule out this interpretation. The findings support the frontal lobe theory of aging by demonstrating that the dysfunction of FM connectivity during memory maintenance may be held responsible for WM memory deficits in aging.

It is if interest to note that both during the oddball and the WM task phase synchronization in the theta band between FM sites and posterior brain regions (parietal, occipital) was shown to decrease with aging. Therefore, this age related deficit could be attributed to a common function required both by the oddball and the WM tasks. These age-related changes of fronto-parietal fronto-occipital networks in the theta band could represent a common mechanism – as assumed by the frontal lobe theory of aging- underlying the changes across wide domains of cognition.

So far, no studies are known in which memory maintenance related EEG connectivity was investigated in association with aging. The successfully maintained trials were accompanied with strengthened coupling within the frontal cortices and between fronto-temporal, fronto-occipital areas. Contrary to that seen in the young, interactions between the MF and lateral frontal cortices, and those between the MF temporal regions related to successful maintenance processes were absent in older adults. The present results are consistent with those of previous studies in which a decline of FM theta power was observed in elderly participants compared to young subjects during a retention period of an episodic word recognition task (Cummins et. al., 2008). An interpretation could be that in the older adults the maximum amount of FM theta connectivity response has already reached its plateau and therefore failed to increase with task-related requirement for efficient WM maintenance. Thus age related deficits on FM theta connectivity in retention period may be due to the dysfunction of the frontal or that of the temporal lobes, or both. There is indirect evidence for both possibilities from an in vivo volumetric study (Raz et al., 2005) in which age related gray matter volume reduction was demonstrated within the lateral frontal cortex and the hippocampus. These findings, together with evidence of increased likelihood of neuropathology in the FM area with age (Johnson et al., 2004; Raz and Rodrigue, 2006 for review; West, 1999), strongly suggest that at least some of the age-related memory deficits are due to changes in the FM cortex.

The present findings support our hypothesis that FM theta connectivity corresponding to the maintenance period is generally decreased in the elderly and may have an impact on age related WM decline. In line of the present observations reduced activation was seen in neuroimaging studies in older compared to young adults in the frontal cortex in memory tasks (Cabeza et al., 2000; Grady et al., 2003). The observed decrease in FM theta connectivity in the elderly could be interpreted in a way that the elderly fail to keep all of the item representations in the focus of attention during the period of maintenance because of inefficient recruitment of the WM related networks, in line with the processes proposed Cabeza (2004).

It should be noted that scope of the present study was focusing on the slow frontal midline theta rhythm, although other (alpha, beta and gamma) frequency bands may also play a potential role in memory processes. The investigation of memory maitenance processes in relation with aging could be extended to these frquency bands in further studies.

5. Conclusions

In the present study the retention period of a WM task was found to be associated with increased FM theta connectivity which supports the role of midline frontal influences in this period. Our data indicate that FM theta networks are an essential neuronal signature for the efficiency of WM maintenance in addition to the WM capacity. Characteristics of the fronto-temporal coupling were predictive for the efficiency of maintenance, and not sensitive for the modulation of memory load, while fronto-parietal connectivity corresponds to the amount of information to be held in WM even when item recognition fails. The present results suggest an age-dependent functional decline of the FM region to sustain a memory maintenance specific connectivity network. These findings may reflect a failure of FM interactions to efficiently recruit other cortical (such as the lateral frontal and temporal regions) during memory maintenance thereby leading to age related behavioral deficits in the memory domain. The findings support the frontal lobe theory of aging by demonstrating that the dysfunction of FM connectivity during memory maintenance may be held responsible for WM memory deficits in aging.

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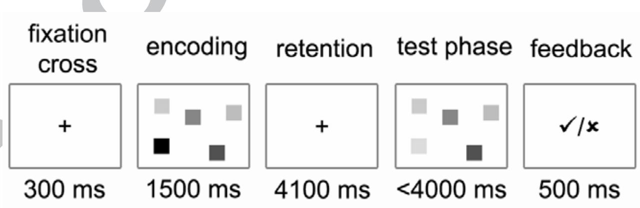
Figure captions

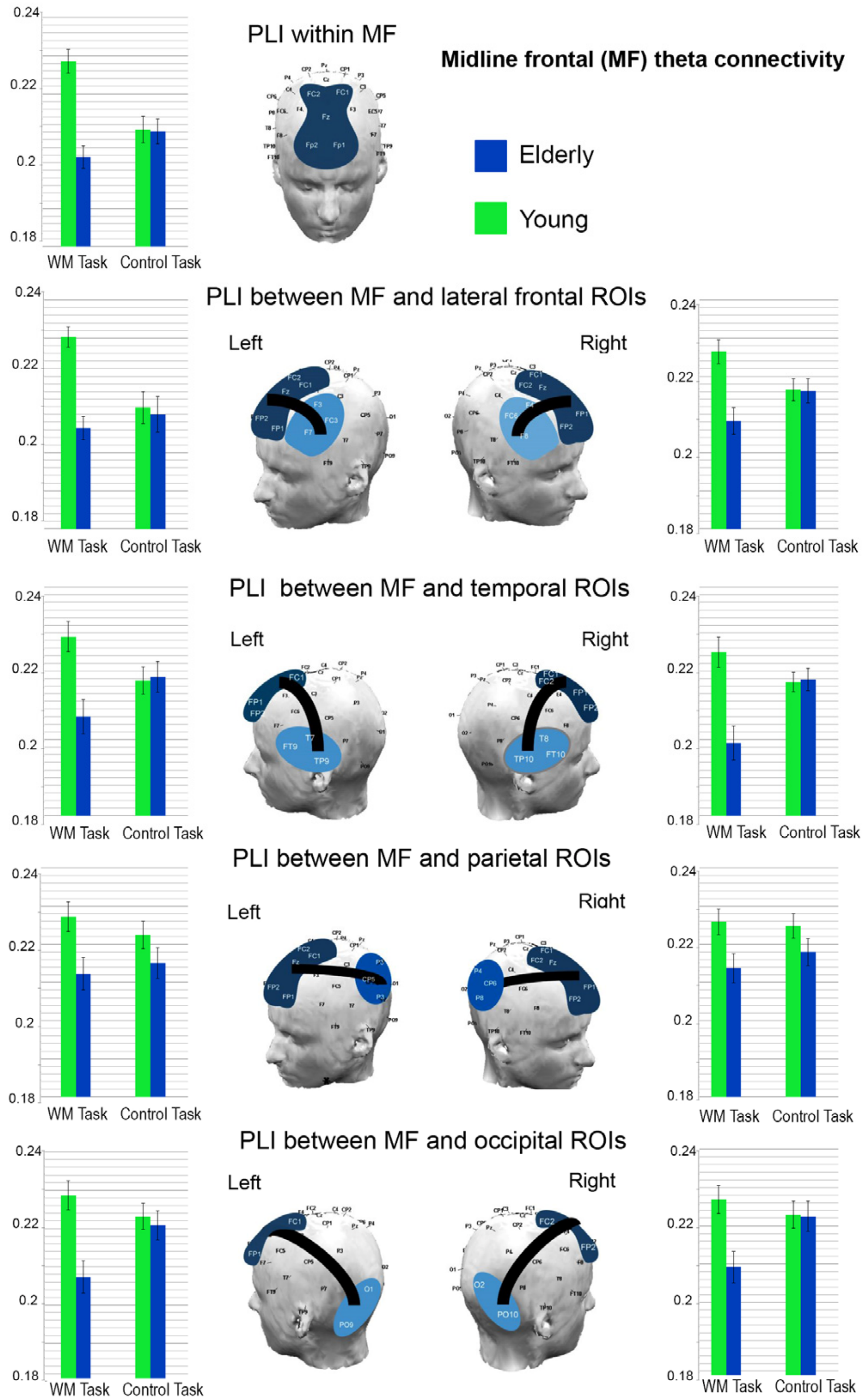
Figure 1. The structure of a delayed match to sample task.

Figure 2. Frontal midline theta connectivity related to WM maintenance period relative to control task. Marked regions in the head plots represent the analyzed locations. Each diagram corresponding to the head plots show FM theta connectivity results of ROIs (shaded areas). Vertical bars show standard error. Significance values are detailed in the text.

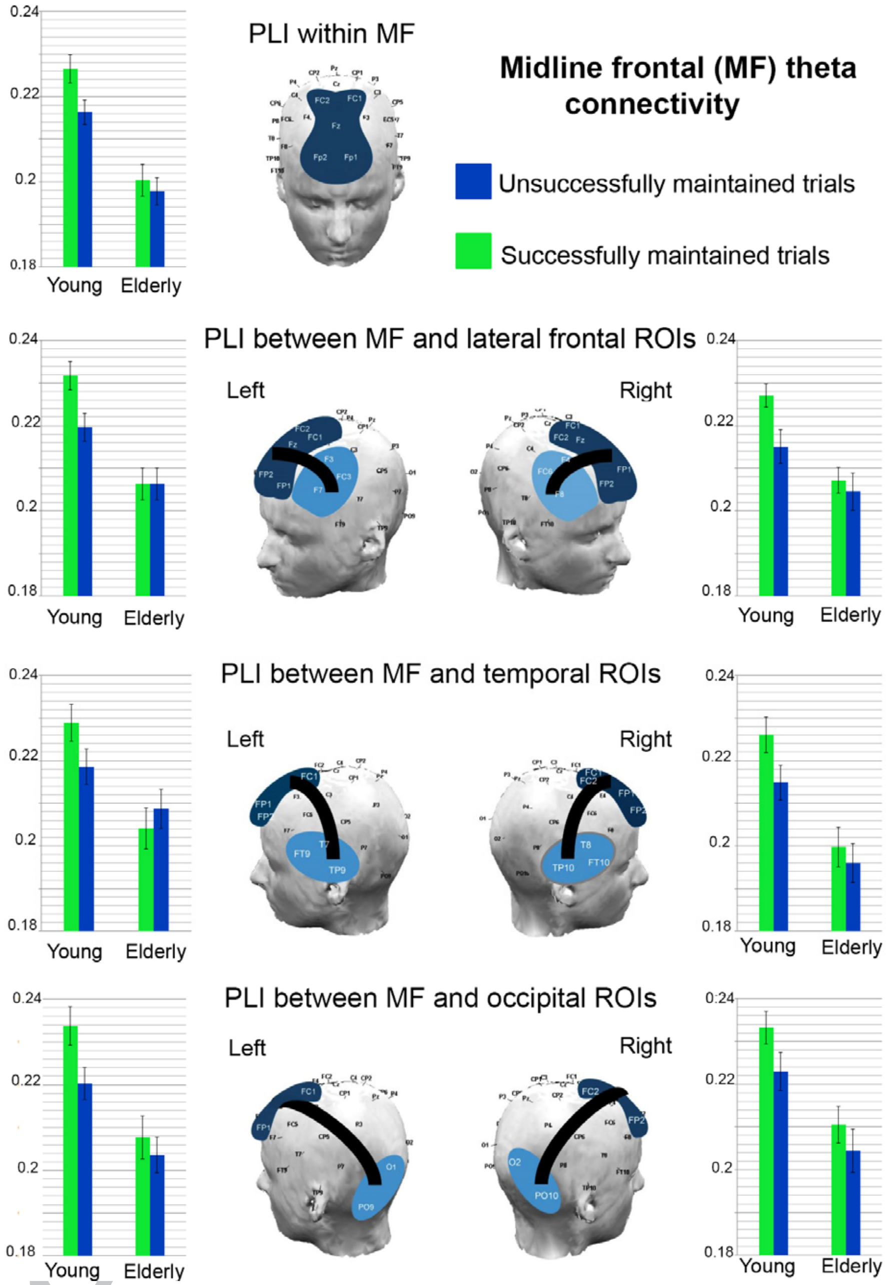
Figure 3. Frontal midline theta connectivity related to WM load. Marked regions in the head plots represent the analyzed locations. Each diagram corresponding to the head plots show FM theta connectivity results of ROIs (shaded areas). Vertical bars show standard error. Significance values are detailed in the text.

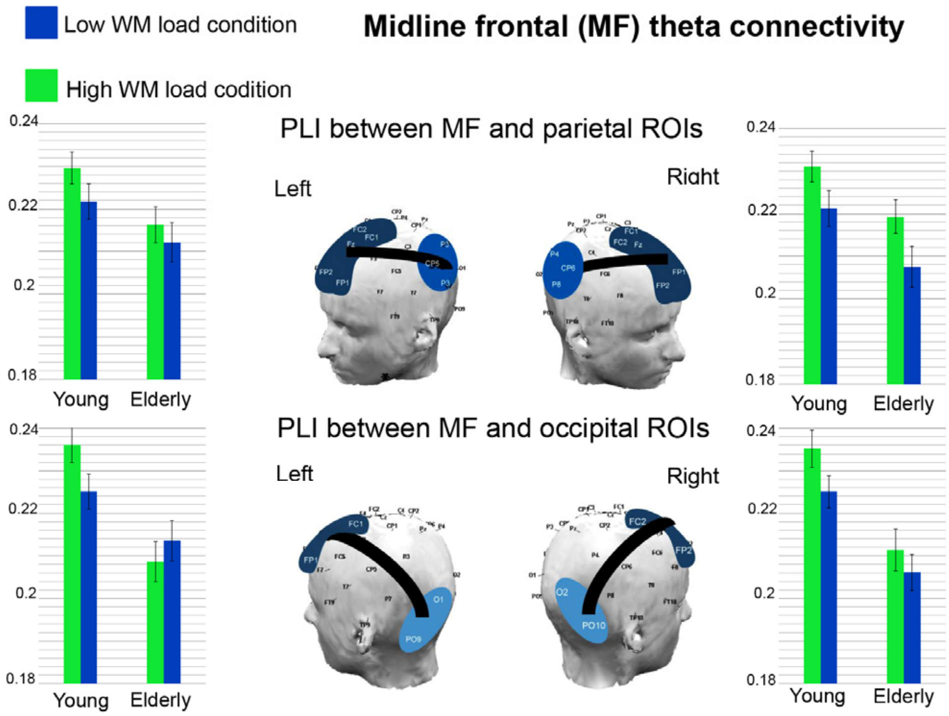
Figure 4. Frontal midline theta connectivity related to efficiency of WM maintenance. Marked regions in the head plots represent the analyzed locations. Each diagram corresponding to the head plots show FM theta connectivity results of ROIs (shaded areas). Vertical bars show standard error. Significance values are detailed in the text.





Midline frontal (MF) theta connectivity
Elderly
Young
PLI within MF
PLI between MF and lateral frontal ROIs
PLI between MF and temporal ROIs
PLI between MF and parietal ROIs
PLI between MF and occipital ROIs
Left
Right
WM Task
Control Task
0.24
0.22
0.2
0.18


PLI within MF
Midline frontal (MF) theta connectivity
Unsuccessfully maintained trials
Successfully maintained trials
PLI between MF and lateral frontal ROIs
Left
Right
PLI between MF and temporal ROIs
Left
Right
PLI between MF and occipital ROIs
Left
Right
0.24
0.22
0.2
0.18
Young
Elderly


Low WM load condition
High WM load codition
Midline frontal (MF) theta connectivity
PLI between MF and parietal ROIs
Left
Right
PLI between MF and occipital ROIs
Left
Right
0.24
0.22
0.2
0.18
Young
Elderly

WM performance on vDMTS task				
	Low (3 Items) WM load		High (5 Items) WM load	
	Mean	SD	Mean	SD
Accuracy (%)				
Young	94.26	±4.61	81.67	±6.98
Old	82.94	±11.06	65.61	±9.81
RT (ms)				
Young	896.25	±191.95	1091.90	±253.11
Old	1049.57	±207.85	1200.98	±378.81

Table 1. Response accuracy and reaction time data in the young adult and in the older adult groups during the vDMTS task

Digit span task performance						
	Overall score		Forward score		Backward score	
	Mean	SD	Mean	SD	Mean	SD
Young	12.3	±2	6.75	±1.019	5	±0.79
Old	10	±1.75	6.06	±1.063	4.06	±0.85

Table 2. Raw scores on the digit span task (WAIS-R) in the young and old groups

		r	r2	t	p
Accuracy	Midline frontal (MF)	0,522	0,272	3,566	0,001
	MF-left frontal	0,538	0,289	3,724	0,001
	MF-right frontal	0,566	0,321	4,007	<0,001
	MF-left temporal	0,587	0,344	4,225	<0,001
	MF-right temporal	0,546	0,298	3,798	<0,001
	MF-left parietal	0,366	0,134	2,2904	0,028
	MF-left occipital	0,476	0,226	3,152	0,003
	MF-right occipital	0,428	0,183	2,762	0,009
Digit span	MF-right parietal	0,339	0,114	2,100	0,043
	MF-right occipital	0,290	0,084	1,767	0,086

Table 3.: Results of the correlation analysis between the individual accuracy / digit span task and the connectivity within and between the midline frontal region and all other ROIs

Highlights

- Age related alterations of EEG functional connectivity was investigated
- EEG recorded during the delay period of a working memory task was analyzed
- The phase lag index was used to assess fronto-midline theta band connectivity
- Frontal midline theta connectivity was sensitive to memory load and later performance
- Decreased level of fronto-cortical connectivity was found in the elderly