Research report

The effects of working memory training on functional brain network efficiency

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Abstract

The human brain is a highly interconnected network. Recent studies have shown that the functional and anatomical features of this network are organized in an efficient small-world manner that confers high efficiency of information processing at relatively low connection cost. However, it has been unclear how the architecture of functional brain networks is related to performance in working memory (WM) tasks and if these networks can be modified by WM training. Therefore, we conducted a double-blind training study enrolling 66 young adults. Half of the subjects practiced three WM tasks and were compared to an active control group practicing three tasks with low WM demand. High-density resting-state electroencephalography (EEG) was recorded before and after training to analyze graph-theoretical functional network characteristics at an intracortical level. WM performance was uniquely correlated with power in the theta frequency, and theta power was increased by WM training. Moreover, the better a person’s WM performance, the more their network exhibited small-world topology. WM training shifted network characteristics in the direction of high performers, showing increased small-worldness within a distributed fronto-parietal network. Taken together, this is the first longitudinal study that provides evidence for the plasticity of the functional brain network underlying WM.

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1. Introduction

Our perceptions, thoughts and experiences are the result of dynamic interactions emerging between functionally specialized areas of the human brain (Fornito et al., 2010). A better comprehension of human cognitions will only be feasible once we comprehend how these interactions are coordinated and organized. Recent studies have shown that the functional and anatomical features of this network are organized in an efficient small-world manner (Bassett and Bullmore, 2009;
Typical features of small-world networks are high clustering coefficients and low characteristic path lengths (Watts and Strogatz, 1998). A high clustering coefficient is characterized by a high level of local neighborhood clustering, which is responsible for efficient local information processing. A low path length characterizes a high level of global communication efficiency (Achard and Bullmore, 2007; Bullmore and Bassett, 2011; Sporns and Zwi, 2004).

In this study, we are interested in the functional network organization underlying working memory (WM) performance. WM is defined as the ability to maintain and manipulate information for higher order cognition (Baddeley, 2003, 2002; Jonides et al., 2008). It has been shown to be crucial for daily life skills, such as reading comprehension (dejonge and dejong, 1996), planning and problem-solving (Shah and Miyake, 1999), and to learn new skills (Pickering, 2006). The involvement of fronto-parietal regions in WM tasks was shown with different neuroimaging methods such as the intracranial electroencephalography (Meltzer et al., 2008; Raghavachari et al., 2006), functional magnetic imaging (Owen et al., 2005) and transcranial magnetic stimulation (Oliveri et al., 2001).

Whether individual differences in WM ability are related to a specific small-world network organization has not been studied so far. Further, it is unclear to date whether WM related small-world networks can be changed and optimized by WM training. In general, there is no study investigating the possible adaptive capacity of small-world networks.

Here we calculated small-world properties of functional brain networks on the basis of high-density EEG coherence measures on an intracortical level. Previous EEG studies showed increased theta-band coherence in frontal and parietal regions during a difficult WM task (Sauseng et al., 2005). Patients with a WM deficit, such as those suffering from Alzheimer’s disease or schizophrenia, exhibit reduced fronto-parietal EEG coherence mainly in theta (Babiloni et al., 2004b; Ford et al., 2002; Hogan et al., 2003; Uhlhaas and Singer, 2006; Winterer et al., 2003). Therefore, we expected small-world characteristics in the functional network within the theta band to reflect individual differences and training effects on WM. Our first hypothesis is that the functional small-world topology of theta-band coherence varies between individuals as a function of WM performance. Second, we anticipate a change in the theta band based small-world topology as a consequence of an intensive WM training, especially in parietal and frontal regions. Because some studies also identified relationships between WM and other frequencies (Hsieh et al., 2010a; Polania et al., 2011), we did not limit our analysis to the theta band, but rather performed the analyses for the whole frequency spectrum.

2. Methods

2.1. Subjects

Sixty-six young adults participated in the study. Thirty-four (mean age: 23 ± 3.86, 21 females) trained on three WM tasks, representing the three functional categories of the WM model of Oberauer et al. (2003). An active control group of 32 subjects (mean age: 23 ± 3.86, 21 females) practiced tasks with low WM demand. Participants were assigned to the two groups at random. The two groups were matched according to age, gender, experience using a computer, and cognitive activity in daily life. Furthermore, there were no pre-training baseline differences in WM composite score, EEG (theta power) and small-world indices (clustering coefficient, path length, degree). The corresponding statistical values are reported in the appropriate result sections. All subjects were consistently right-handed according to the Annett-Handedness-Questionnaire (Annett, 1970), and highly proficient Swiss German or German Speakers. Subjects reported no history of psychiatric or neurological disease, neuropsychological problems, or medication and drug abuse. All gave written informed consent to participate in the study. This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Institutional Review Board of “Kantonale Ethikkommission” (EK: E-80/2008). For various reasons, such as drop out, technical problems during EEG recording, or insufficient valid EEG data, six participants were discarded from further analysis, leading to a total of 60 remaining data sets (30 per group).

2.2. Training

Participants trained extensively for four weeks, about 30 min in each session (20 sessions in total). Training was self-administered at home via the software Tatool (von Bastian et al., in press-b), a Java based open-source training and testing tool. After each training session, training data were automatically uploaded to a webservice running Tatool Online. Tatool Online allows monitoring training progress and participants’ commitment constantly. For example, session duration and percentage correct were automatically analyzed online to detect any obvious irregularities.

The training tasks were based on the facet model of WM capacity (Oberauer et al., 2000, 2003), which assumes three functional categories of WM capacity: storage and processing, executive processes, and relational integration. Storage and processing is defined as the simultaneous maintenance and manipulation of information. Executive processes involve the selective activation of relevant representations and the suppression of irrelevant distracting ones. Relational integration is defined as the coordination of information elements into structures (Oberauer et al., 2000, 2003). The WM group trained one task per functional category of the WM model. We chose the training tasks based on a previous study examining effects of training the three functional categories separately (von Bastian and Oberauer, in press). To train storage and processing, we used a numerical version of a complex span task (cf. Daneman and Carpenter, 1980), in which participants had to memorize and recall lists of two-digit numbers. In between two successive memoranda, participants had to complete a distracting task, in which they had to decide whether a single digit shown was odd or even. Executive processes were trained using the task-switching paradigm (Monsell, 2003). In this task, participants had to categorize bivalent figural stimuli (simple geometric shapes) according to two different rules that changed every second trial. The stimuli and the corresponding set of rules were replaced every fifth session to enhance variability of the task. Relational integration was
trained by a self-constructed task (“tower of fame”), in which participants had to imagine a building with apartments on several floors. Sentences were presented sequentially, giving information about which famous person lives in which apartment (e.g., “Tom Cruise lives on the second floor in apartment A”). This statement then disappeared and was followed by a second statement (e.g., “Britney Spears lives two floors above in the apartment vis-a-vis”). At the end, participants had to recall which famous person lives where. For an illustration of the trained WM tasks see Fig. 1.

To evaluate effects of a training intervention, it is crucial to compare the trained group to an active control group. This differentiates training effects not only from repetition effects, but also from intervention effects (e.g., effects of regular computer use), and expectancy effects (Oken et al., 2008). For the latter purpose it is important that the alternative training is perceived by participants as a potentially effective cognitive training. To control for placebo effects, training conditions for the control group were identical to those of the intervention group. Therefore, participants in the control group trained the same amount of time. The active control group practiced tasks with low WM demand, which were a knowledge quiz and two visual-search tasks (circle-task, digit-task). The quiz was composed of questions on general knowledge, each with four response options, one of them was correct. In the “circle-task”, all circles displayed in each search array had two gaps, except for one circle that had only one gap. The task was to find this deviant circle and to indicate the direction of the gap by pressing the respective arrow key on the keyboard. In some trials, all circles had two gaps, in this case participants had to press “A”. In the “digit-task”, rows of identical digits were presented on the screen. Each digit should be presented as often in a row as the digit indicated (e.g., 55555, 333). The subjects had to check whether this rule was broken (i.e., a digit was presented too many or too few times), and press the number key indicating the digit that broke the rule. For example, if there was a block of six “5”’s in a row, participants had to press the “5” on the keyboard.

For all training tasks, difficulty was adapted stepwise to individual performance through the adaptive algorithm provided by Tatool (von Bastian et al., in press-b). The algorithm set an individual benchmark between 80% and 90% based on the performance of the participant after 40% of the number of trials in each session. If the participant’s performance in the following 40% of the trials (counted across training sessions) was greater than the individual benchmark, task difficulty was increased, and a new individual benchmark was set after the next 40% of trials. However, if performance was lower than the benchmark for three times in a row, task difficulty was decreased. For example, in the complex span task, the number of memoranda was raised with increasing performance.

Fig. 1 – WM training tasks. Illustrated are the WM training tasks, which were trained by the WM group.

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2.3. Tasks for pre-test and post-test

Before and after the training intervention, participants were invited to the Department of Psychology. All subjects completed a cognitive test battery covering different aspects of WM and reasoning. Half of the participants in each intervention group completed a broad cognitive test battery before the EEG resting recordings, and half of the participants completed it afterward. There were no effects of order on behavioral and electrophysiological data, and order was not analyzed further. Overall, the test battery comprised test versions of the three WM training tasks, three structurally similar WM tasks with different materials (verbal complex span task to measure storage and processing, verbal task switching to measure executive functions, and kinship integration to measure relational integration), two matrix reasoning tasks to measure fluid intelligence, and a control task to which we did not expect any transfer (quiz on general knowledge). The complete behavioral results of test battery will be reported elsewhere (von Bastian et al., in press-a). In this study, we focus on the WM training tasks and the structurally similar transfer tasks. The test versions of the complex span task comprised 15 trials with list lengths (i.e., number of elements to memorize) ranging from three to seven. In the verbal version of the complex span task, memoranda were words, and the distracting processing task was to decide whether a letter presented was a consonant or a vowel. The tests to measure task switching comprised 80 trials of bivalent stimuli. As in the training, task switches occurred in alternating runs of two. In the figural version of the task, participants had to either categorize the stimuli as blue or green objects, or as being round or angular. In the verbal version, stimuli were words shown on the screen. Participants had either to categorize the font color of the words (green or blue) or to decide whether the word was a river or a city (e.g., London or Thames). The test version of the “tower of fame” task comprised 18 trials with the number of sentences (i.e., information elements to be integrated) ranging from two to four. The other task used to measure relational integration was the kinship integration task (cf. von Bastian and Oberauer, in press). As in the “tower of fame” task, single relational statements were presented sequentially. In the kinship task, these were verbal descriptions of the relationship between two people (e.g., “Anne is Barbara’s sister”, “Barbara is Charlie’s mother”). Participants were then asked to indicate the implied (but not explicitly described) relationship between two of the people mentioned in several consecutive sentences (e.g., “Anne is Charlie’s?” with the correct answer being “aunt”). Participants had to complete 16 trials with the number of sentences varying between two and three.

To obtain a single WM capacity measure we first conducted a factor analysis. This factor analysis yielded a solution with two factors with an eigenvalue >1. Whereas storage and processing tasks and the relational integration tasks all loaded similarly strongly on Factor1 (eigenvalue = 2.86, explained variance = 71.59%), the executive processes tasks loaded on the Factor2 (eigenvalue = 1.48, explained variance = 11.7%). The factor loadings were the following: Factor1: storage and processing (numerical: $r = .799$, verbal: $r = .735$), relational integration (tower of fame: $r = .761$, kinship task: $r = .758$) and executive processes (figural: $r = .048$, verbal: $r = .176$; Factor2: storage and processing (numerical: $r = -.017$, verbal: $r = .251$), relational integration (tower of fame: $r = .229$, kinship task: $r = .391$) and executive processes (figural: $r = .693$, verbal: $r = .376$). This factor structure confirmed findings from previous studies showing that the two functional categories storage and processing and relational integration are more strongly related to each other than to executive processes (Oberauer et al., 2003). Moreover, the WM training group did not show any performance improvements in the executive processes tasks. Therefore, our WM capacity measure was a composite score calculated by averaging the performance only in the tasks measuring storage and processing (numerical and verbal complex span) and relational integration (tower of fame and kinship task). For this WM composite score, we calculated a repeated measure $2 \times 2$ analysis of variance (ANOVA) with the between-subject factor Group (WM group, control group) and within-subject factor Time (pre-training, post-training). For ANOVAs which exceeded the statistical threshold of $p < .05$, subsequently Bonferroni–Holm adjusted post-hoc t-tests were applied ($p < .05$).

2.4. Electroencephalographical recording

The EEG measurements took place in a sound-shielded Faraday cage. We instructed the subjects to sit comfortably in the chair and to rest with their eyes alternately open or closed during EEG acquisition. The EEG protocol consisted of the participants resting with eyes open for 20 sec, followed by 40 sec with their eyes closed; this was repeated five times. Only the data from the eyes-closed periods were analyzed, because they were of higher quality, resulting in a total of 200 sec ($5 \times 40$ sec) of eyes-closed EEG data. High-density EEG was recorded at a sampling rate of 500 Hz with a bandpass of 1–100 Hz with a 256-channel EEG Geodesic Netamps system (Electrical Geodesics, Eugene, Oregon). Recording reference was at Cz (vertex of head). Impedances were kept below 30 kOhm. Independent component analysis was used to remove eye movement artifacts from the EEG. In addition to the application of an automated artifact rejection procedure, data were all visually inspected for noise eye movements, eye blinks, sweating, and muscular artifacts. After artifact rejection, the electrodes in the outermost circumference (chin and neck) as well as other artifact channels were excluded and interpolated to a standard 204 electrode array (Britz et al., 2009). The artifact-free EEG was recomputed against the average reference and segmented into 2 sec epochs. In a second step a discrete Fourier transformation algorithm was applied to the artifact-free 2 sec epochs (68 segments per subjects). The power spectrum of 1.5–49.5 Hz (resolution .5 Hz) was calculated. The spectra for each channel were averaged over all epochs for each subject.

2.5. Scalp-map analysis

2.5.1. Analysis of the neural correlates of WM capacity

For the investigation of the neural correlates of WM, by analyzing only the pre-training data, we included all 60 subjects in
a regression analysis. We conducted the analysis according to our previous study (Langer et al., 2012). To this end, data of the 204 electrodes were collapsed into three anterior and three posterior electrode clusters: anterior (left, middle, right), posterior (left, middle, right). Each cluster consisted of 28 electrodes. Several electrodes could not be classified certainly to a cluster and therefore they were excluded from the electrode cluster analysis. The absolute power spectra were integrated in the following independent frequency bands following classification proposed by Kubicki et al. (1979): delta (1.5–6 Hz), theta (6.5–8 Hz), alpha1 (8.5–10 Hz), alpha2 (10.5–12 Hz), beta1 (12.5–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30–49.5 Hz). We ran the regression analysis between the pre-training WM capacity measure and the EEG power spectra of each cluster and frequency band. Statistical significance was assessed by means of a non-parametric randomization test (Nichols and Holmes, 2002). An error probability of \( p < .05 \) (corrected for multiple comparisons across all frequencies and electrode clusters) was used to indicate significant correlations.

2.5.2. Analysis of the neural effects of the WM training
For the investigation of the effects of the WM training, the proportional change in EEG power between pre- and post-training (post-training/pre-training \( \times 100 \)) was computed for each subject, electrode, and frequency bin. The proportional change, also called percent signal change, is a frequently used measure (Dietz et al., 2009; Takahashi et al., 2005; Babiloni et al., 2004a; Lehmann et al., 2006; Mulert et al., 2004; Sinai and Pratt, 2003). Therefore, we conducted our graph-theoretical network analysis on the basis of intracerebral brain oscillations. We are aware that the precision of the EEG-source localization is limited. Nevertheless, we argue that the source reconstruction used in the present study (Pascual-Marquès, 2002) is informative because it has been experimentally validated in various studies and under diverse conditions (Khateb et al., 2001; Langer et al., 2010; Pizzagalli et al., 2000), and it has been cross-validated with functional magnetic resonance imaging (fMRI) (Seeck et al., 1998; Worrell et al., 2000). For the estimation of the intracerebral electrical sources that generated the scalp-recorded activity, we used standardised low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marquès, 2002), freely available at [http://www.uzh.ch/keyinst/loreta.htm](http://www.uzh.ch/keyinst/loreta.htm). Based on the recorded scalp electric potential differences, sLORETA calculates the three-dimensional distribution of the electrically active neuronal generators in the brain as standardised units of current density (A/cm²) at each voxel by assuming similar activation among neighboring neuronal clusters (Pascual-Marquès, 2002). In the current implementation of sLORETA, computations were made in a realistic head model (Mazziotta et al., 2001), with the three-dimensional solution space restricted to cortical gray matter, as determined by the probabilistic Talairach atlas (Lancaster et al., 2000). The standard electrode positions on the MN1152 scalp were taken from Jurcak et al. (2007) and Oostenveld and Praamstra (2001). The intracerebral volume is partitioned into 6239 voxels at 5 mm spatial resolution. Thus, sLORETA images represent the standardized electric activity at each voxel in neuroanatomic Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. sLORETA estimates the inverse problem by taking into account the well-known effects of the head as a volume conductor. The 2-sec epochs of the preprocessed EEG data of each subject were imported into the sLORETA software. To subdivide the entire brain into separate regions, the current density was measured in 42 anatomical regions of interest (ROIs) in each hemisphere, which were defined according to Brodmann areas (BAs) (Brodmann, 1909). sLORETA estimates the solution of the inverse problem based on the assumption that the smoothest of all possible activation distributions is the most plausible one. This assumption is supported by neurophysiological data demonstrating that neighboring neuronal populations show highly correlated activity. Because of this assumption of sLORETA, we took just the single center voxel of each ROI to reduce possible contamination of non-physiological connectivity between the ROI’s, as we did in our previous study (Langer et al., 2012).

Within the sLORETA analysis framework, coherence between the 84 anatomical ROIs in both hemispheres was computed. Coherence was calculated as linear instantaneous instantaneous coherence. This measure was used in other studies before (Langer et al., 2012; Jancke and Langer, 2011; De Vico Fallani et al., 2010) and is deemed an adequate measure for...
computing resting state networks. Mathematical details can be found in Pascual-Marqui (2007), here we give a brief description. The linear instantaneous connectivity is a general measure that operates in the frequency domain. This measure ranges between 0 in the case of independent times series, and 1 in the case of maximally synchronous signals. Given two signals $x$ and $y$, the linear instantaneous connectivity is calculated for a particular frequency $f$ by taking the square of the cross-spectrum $|S_{xy}(f)|^2$ and by dividing the product of the two corresponding auto power spectra:

$$SC_{xy}(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)}$$

In contrast to the classical coherence measure, the coherence measure used in the present study is an amplitude-independent measure due to the division of the product of the corresponding power spectra, which eliminates the role of the amplitude. This is important because training-induced changes in power could result in artifactually larger local or long-range connectivity measures when using the classical coherence measure. This artifact is avoided by using an amplitude free coherence measure, which is not biased by power changes. Intracerebral coherence measures of the 84 ROIs were subjected to graph-theoretical network analysis. An individual network is represented by the weighted connectivity matrix with nodes and edges, where nodes represent ROIs and edges represent the undirected weighted connections (correlations) between the signals of ROIs.

Because there is currently no generally accepted strategy for applying a particular threshold on correlations matrices, we thresholded repeatedly over a wide range of correlation thresholds in increments of $r = .05$ from $r = .65$ to $r = .95$. The so obtained thresholded connectivity matrices were then subjected to the network analysis software tnet (Opsahl and Panzarasa, 2009; Opsahl, 2009) to quantify small-worldness indices (Watts and Strogatz, 1998; Bullmore and Sporns, 2009). The typical key characteristics of small-world networks were computed, including the clustering coefficient, the characteristic path length and the degree centrality measures (analyzed in the regional node analysis section) (Watts and Strogatz, 1998). The clustering coefficient is given “by the ratio between the number of connections between the direct neighbors of a node and the total number of possible connections between these neighbors” (Watts and Strogatz, 1998). The characteristic path length of a network gives “the average number of connections that have to be crossed to travel from each node to every other node in the network” (Watts and Strogatz, 1998).

2.7. Regional node analysis

In order to identify and discriminate important hub regions within the small-world network, weighted degree centrality measures were calculated for each individual node and plotted as degree distribution (Opsahl and Panzarasa, 2009; Freeman, 1978). Degree (which is a particular centrality measure) is defined as the number of connections of a node (i.e., the sum of weights of the edges connected to a particular node). Therefore, each node is characterized by its own degree value. To visualize the degree values graphically, we used the MATLAB toolbox BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

In the same manner to the scalp-map analysis of EEG power, a regression analysis and statistical comparisons between groups and conditions were conducted. To investigate the neuronal correlates of WM, only the pre-training data were analyzed. Each participant’s pre-training WM performance was correlated with that participant’s small-world indices (clustering coefficient, path length) and their weighted degree centrality at each ROI. In order to investigate the effects of the WM training, a $2 \times 2$ repeated measure ANOVA with the between-subject factor Group (WM training group, control group) and the within-subjects factor Time (pre-training, post-training) was computed for each small-world index. For the significant main effects, we employed post-hoc $t$-test with a significance level of $p < .05$ (Bonferroni–Holm corrected for multiple comparisons) (Holm, 1979; Shaffer, 1995).

For the regional node analysis (degree centrality measure), we investigated the effects of the WM training analogically to the training effects in the scalp-map analysis by computing the proportional change of the degree centrality between pre- and post-training (post-training/pre-training $\times$ 100). The proportional-change score eliminates the interindividual differences in degree centrality, such that the analysis focuses only on the intraindividual change induced by the WM training. First, we compared proportional change of degree centrality within each group separately by one-sample $t$-tests. Then we investigated through a two-sample $t$-test, whether the pre–post change in degree centrality differed between groups. For the regional node index, error probability was set to $p < .05$, uncorrected for multiple comparisons. Because of our strong a priori hypothesis predicting training-related changes in the fronto-parietal network, we did not use a correction for multiple comparisons for the regional node index analysis.

3. Results

3.1. Behavioral results

A WM capacity score was computed for each subject and time point by averaging z-transformed scores from the tasks measuring storage and processing (numerical and verbal complex span) and relational integration (tower of fame, kinship test); for a description of these constructs see Oberauer et al. (2007). Behavioral data showed that WM training led to significant improvements in the trained as well as some non-trained tasks (see von Bastian et al., in press-a). This pattern was also reflected in the composite score used for this study, where we used a repeated $2 \times 2$ ANOVA ($n = 60$) with the between-subjects factor Group (WM training group, control group) and the within-subjects factor Time (pre-training, post-training). First of all, we found no significant baseline differences for the WM composite score in the pre-training session between the two groups ($t = .81, p = .42$). But we found a significant main effect of Time ($F = 94.00, p = 1.38 \times 10^{-13}$) and an interaction effect ($Time \times Group, F = 7.97, p = .007$). The subsequent post-hoc $t$-tests (two-sided, $n = 60$) revealed...
significant superior performance in the post-training session for the WM training group compared to the control group ($t = 2.77, p = .008$, corrected for multiple comparisons). Furthermore, there was a significant increase from the pre- to the post-training session in WM composite score for the WM training group ($t = -8.36, p = 4.34 \times 10^{-5}$ corrected for multiple comparisons) and the control group ($t = -4.80, p = .77 \times 10^{-5}$, corrected for multiple comparisons). The complete behavioral results of the test battery will be reported elsewhere (von Bastian et al., in press-a).

3.2. Scalp-map analysis of EEG power

We investigated the neural correlates of WM performance before training across all frequency bands. The only positive correlation was observed with theta power in the right anterior electrode cluster ($r = .33, p = .037$, corrected for multiple comparisons) (Fig. 2A). The other electrode clusters in the theta band also revealed strong correlations, but they were not significant after corrections for multiple testing. The scalp map distribution of the correlation between WM performance and the theta power is shown in Fig. 2B.

The investigation of the WM training effects on the EEG power electrode cluster analysis revealed significant changes from pre- to post-training session only in the WM training group ($n = 30$), namely in the theta power in left anterior ($t = 3.92, p = .008$, two-sided) and middle anterior ($t = 4.00, p = .004$, two-sided) electrode clusters (corrected for multiple comparisons) (Fig. 3). The other electrode clusters in the theta frequency also showed alterations, but these changes did not survive the multiple comparisons adjustment. No electrode cluster significantly changed in the control group (Fig. 3). The analysis of the pre-training group comparison revealed no significant effects, indicating no baseline differences between the two groups (electrode cluster: anterior left: $t = -4.9, p = .04$; anterior middle: $t = -4.6, p = .04$; anterior right: $t = -5.2, p = .46$; posterior left: $t = -17, p = .89$; posterior middle: $t = -5.8, p = .57$; posterior right: $t = -9.3, p = .43$, two-sided). The comparison regarding differences between the two groups in the proportional change from the pre- to the post-training session in the EEG power spectra revealed strong effects in the theta frequency, but they also did not survive the correction for multiple comparisons (Fig. 3). By comparing the EEG power between the pre- and post-training sessions the question might arise whether different signal-to-noise ratios between the pre- and post-training session could explain the results. But the possibility of a signal-to-noise induced change during the post-training session is very unlikely for two main reasons. If the above-mentioned critique would hold true the signal-to-noise ratio would only affect the WM group, which is not reasonable. Second, the strong increase is primarily found in the theta band and not in the other frequency bands, which is also an additional argument against the signal-to-noise ratio effect. Furthermore, statistical significant effects were only found in two of the six electrode clusters in the theta band, which demonstrates that the theta power changes induced by WM training are not present across all electrodes but rather at very specific topographical positions. We also localized the significant theta-power effects with sLORETA. The source localization of the neural correlates of the theta band we therefore focused on the graph-theoretical network analysis on the theta frequency band. The graph-theoretical network analysis on the intracortical level revealed nearly

Fig. 2 – Scalp-map analysis of pre-training measurements. The correlation between WM performance and the EEG power on the electrode level for all frequencies in the pre-training measurements is displayed. (A) The correlation between WM performance and the six electrode clusters is displayed for eight frequency bands. Each bar group represents one frequency band. The six bars in each frequency band represent the six electrode clusters (ordered: anterior left, anterior middle, anterior right, posterior left, posterior middle, posterior right). The Fischer's permutation test revealed a significant relationship only in the right anterior cluster of the theta band ($p < .05$, corrected for multiple comparisons, $n = 60$). (B) The distribution of the correlation coefficients over the scalp is displayed for the theta frequency. The significant anterior middle electrode cluster contains the following electrodes from the 256-channel EEG Geodesic system (E9; E186; E17; E8; E198; E24; E16; E7; E207; E30; E23; E15; E6; E215; E29; E22; E14; E5; E28; E21; E13; E34; E27; E20; E12; E33; E26; E19).

WM performance and the WM training effects are summarized in Supplemental Figs. S1 & S2 and Tables S1 & S2.

3.3. Graph-theoretical network analysis

Because of our hypothesis regarding the relationship between WM and theta oscillations as well as the results of the scalp-map analysis, which revealed significant effects in the theta band we therefore focused on the graph-theoretical network analysis on the theta frequency band. The graph-theoretical network analysis on the intracortical level revealed nearly
identical results for all thresholds, hence, we only report the results for the threshold of $r = .85$. This threshold is based on our previous studies showing that the network with a threshold at $r = .85$ represents the most adequate small-world topology (Jancke and Langer, 2011; Langer et al., 2012). The results of the other thresholds are summarized in Supplemental Tables S3 and S4. The average network (correlation matrix across all subjects) in the theta frequency is composed of 84 nodes and 1718 edges. For the investigation of the neural basis of WM, again analyzing only the pre-training data, the small-world indices (clustering coefficient, path length) were computed for each subject individually, and correlations between the small-world indices and the WM performance of the pre-training data were calculated. We found a positive correlation for the clustering coefficient ($r = .32, p = .03$), whereas a negative relationship emerged for the path length ($r = -.30, p = .04$, corrected for multiple comparisons) (Fig. 4). There was no correlation between the WM performance and small-world network indices outside the theta band (Supplemental Table S5). To investigate if the correlation between the WM composite score and the small-world indices in the theta band was specific, we performed in addition a correlation between the general knowledge performance and the small-world indices. The small-world indices were not significantly correlated with the quiz on general knowledge (clustering coefficient: $r = .04, p = .74$; path length: $r = .30, p = .71$). These results indicate that the correlations between the small-world indices and the WM performance are very specific.

For the investigation of WM training effects on small-world parameters, we first subjected each small-world index separately to a 2 $\times$ 2 ANOVA with the between-subject factor Group (WM training group, control group) and within-subject factor Time (pre-training, post-training). For the clustering coefficient we found a significant main effect for the factor Time ($F = 6.30, p = .01$) and a significant Time $\times$ Group interaction ($F = 5.44, p = .02$). The post-hoc two-sided $t$-test revealed a significant increase from the pre- to the post-training session in the WM training group ($t = 3.40, p = .002$, corrected for multiple comparisons). In addition, we found a significant difference between the WM training group and the control group in the post-training session. In the post-training session, the WM training group had a larger clustering coefficient than the control subjects ($t = 2.37, p = .02$, corrected for multiple comparisons) (Fig. 5). This difference was not apparent in the pre-training session.
baseline (clustering coefficient: \( t = .92, p = .36; \) path length: \( t = -.051, p = .61 \)).

The ANOVA of the path length showed a significant Group \( \times \) Time interaction (\( F = 6.44, p = .01 \)). The post-hoc two-sided t-test demonstrated a decrease of the path length in the WM training group from the pre- to the post-training session (\( t = -2.12, p = .04 \), corrected for multiple comparisons). Moreover, in the post-training session, the WM training group showed a significantly smaller characteristic path length compared to the control group (\( t = -2.52, p = .02 \), corrected for multiple comparisons) [Fig. 4]. This group difference was not seen at pre-test (\( t = -.51, p = .61 \)).

The investigation of the WM training effects on small-world indicators in the other frequency bands revealed a significant main effect of Time (beta3 and gamma) and a Group \( \times \) Time interaction (gamma) on the clustering coefficient. The clustering coefficient increased from the pre- to the post-training session in the WM training group (Supplemental Table S6).

### 3.4. Identification of hub regions

Degree centrality was evaluated to identify the nodes in the networks that are responsible for the WM performance and WM training effects on the network reflected in theta oscillations. The first analysis, where we investigated the relationship between WM performance and degree centrality in the pre-training session, revealed significant positive correlations between WM performance and degree centrality primarily in the parietal cortex (bilateral), right superior temporal gyrus, the right insular cortex and the right secondary sensory area (visual and auditory). The higher a person’s WM performance, the higher was their degree centrality in these regions. On the other hand, we found significant negative correlations primarily bilaterally in the frontal cortex, the cingulate cortex, as well as the medial temporal lobe and hippocampal regions (see Fig. 6).

The analysis of the WM training effects revealed similar hub regions. In comparison to the control group, the WM training group showed enhanced degree centrality measures after training in the parietal regions, the right superior temporal gyrus and the left inferior frontal gyrus. In contrast, we found a decreased degree centrality in the prefrontal areas, the right entorhinal and premotor cortex in the WM training group compared to the control group (Fig. 7). The statistical values of the degree centrality analyses are summarized in the Supplemental Tables S7 and S8. To rule out that these results are not biased by pre-training baseline differences, we also
compared the degree centrality between the two groups in the pre-training session. We found only one node that differed significantly between the two groups in the pre-training session. The control group had a larger degree centrality in the right BA 2 compared to the WM training group ($t = 2.13, p = .04$). Because this specific node was not significant in any of our other degree centrality analyses, we can affirm that our results are not biased by any pre-training baseline differences.

4. Discussion

This study aimed to extend our knowledge about the plasticity of functional brain networks. We were particularly interested in examining whether intensive WM training could shift the resting-state EEG brain network more toward small-world topology. As argued in a previous paper of our group, the resting state can be regarded as the starting point for subsequent task-related cognitive processes (Langer et al., 2012). Therefore, our hypothesis was that intensive WM training would modify this starting point, as represented by increased small-worldness of the functional brain networks, and that this in turn would be beneficial for subsequent WM performance.

We first determined through an exploratory scalp-map analysis that the power in the theta band was correlated with WM performance, and that power in the theta band was increased by intensive WM training. Thus, we focused our connectivity analysis on theta. We found that a more efficient functional network in the theta band, as indexed by a higher degree of small-worldness, was correlated with higher WM performance before training. We further demonstrated that WM training increased small-world topology in the same functional brain networks. More precisely, in 72% of our subjects the training-induced WM gain was directly related with an increase of the clustering coefficient and a decrease of the path length. In the following we discuss the importance of the theta band for WM, and relate our findings of the network analysis to recent findings in the neuropsychological literature of WM.

4.1. Theta and WM

An analysis across a broad spectrum of frequencies and six electrode clusters revealed that only the theta frequency...
Fig. 7 – Changes in degree centrality induced by WM training. The WM training effects on the degree centrality is illustrated. On the left side, the proportional changes of degree centrality measurements, which were significantly larger (red) or smaller (blue) in the WM training group ($n = 30$) compared to the control group ($n = 30$), are displayed depending on the magnitude of the difference (the darker and bigger the higher the effect). The proportional changes from the pre- to post-training in the degree centrality are presented for the WM training group (middle figure) and the control group separately (right figure). A significant degree of a node is defined by exceeding the significant threshold of $p < .05$ (uncorrected for multiple comparisons, two-sided). Furthermore, the connections of hub regions in which the hubs were significantly different between the WM training group and the control group or between the pre- to post-training within each group are presented as lines between different nodes.
power in the anterior electrodes was correlated with WM performance, and was increased by WM training.

In humans, theta waves are usually in the 4–8 Hz frequency range and have been associated with spatial navigation (de Araujo et al., 2002; Kahana et al., 1999) and WM processing (Klimesch, 1999; Klimesch et al., 1997; Onton et al., 2005; Raghavachari et al., 2006; Sauseng et al., 2005). In a study by Raghavachari et al., cortical theta activity was increased during information encoding and retention in a Sternberg-like WM task (Raghavachari et al., 2001). Moreover, an enhancement of frontal theta activity has been related to increasing WM load (Gevins and Smith, 2000; Jensen and Tesche, 2002; Moazami-Goudarzi et al., 2008). Sauseng et al. suggested that interregional theta synchronization might play an important role in the co-activation of neural structures, which are involved in different sub-processes of complex WM functions (Sauseng et al., 2010). This hypothesis is further supported by Sarnthein et al., who suggest that the prefrontal supervisory system accesses the tempo-parietal modality-specific subsystems by interregional theta coherence (Sarnthein et al., 1998). The theta oscillations are considered a result of an interaction within neuronal networks, mainly in the pyramidal cells of the hippocampus. Several feedback loops connect the hippocampal formation with different cortical regions, the prefrontal cortex in particular (Klimesch, 1999; Miller, 1991; Steriade et al., 1990). In addition, several studies have shown a cross-frequency coupling between theta and higher frequency oscillations (i.e., gamma) (Canolty et al., 2006; Lisman and Idiart, 1995). This might reflect the organization of multiple items into sequential WM representations (Sauseng et al., 2010). The present findings of associations between WM performance and WM training effects with EEG power and small-world network characteristics confirm the important role of theta oscillations for WM functioning. Our additional analyses revealed similar results also in the gamma frequency band. Future studies have to show whether our exploratory findings in the gamma band are replicated, and if so, whether they reflect effects of cross-frequency coupling on small-world characteristics.

4.2. The functional network of WM

We identified a network of coherent theta activity that was associated with higher WM performance before training, and changed during WM training. This network comprises seven main brain regions: the bilateral dorsolateral frontal region (BA 9, 46), the bilateral rostral prefrontal cortex or frontal pole (BA 10, 11), the bilateral (but predominantly right hemispheric) parietal cortex (BA 39/40), the left premotor cortex (BA 6, 8), the right insular cortex (BA 13), the bilateral areas of the limbic system including the entorhinal cortex (BA 28, 34), the posterior cingulated cortex (BA 29, 30, 31) and the secondary sensory areas (BA 22 and BA 19).

This network is characterized by a dissociation between frontal and parietal areas, in line with other WM and intelligence studies (Olesen et al., 2004; Langer et al., 2012). In particular, most of the correlations between WM performance and degree centrality in prefrontal areas and the entorhinal cortex were negative, and the training effects on degree centrality in these areas were also negative. In contrast, we found positive correlations, and increases after training, for degree centrality in parietal regions, the insular cortex and the superior temporal gyrus. This fronto-parietal dissociation is in good agreement with neural-efficiency theory, which postulates that better-performing subjects need less neural resources primarily in the frontal brain regions to solve a cognitive task (Neubauer and Fink, 2009). An alternative explanation for the fronto-parietal dissociation is proposed by the dual-process theory of Chein and Schneider (2005), which postulates a practice-related redistribution of functional activations, such that controlled task performance gradually transitions into automated task performance. This transition is associated with a decrease of neural activity in general control centers (frontal brain regions) but an increase in task specific regions (parietal cortex). In the following, we will briefly discuss these regions within the WM network. Because most studies on WM investigated WM during task execution, we have to relate our findings of the network analysis obtained in the resting state to task-related results. However the resting state may reflect neurophysiological activations that consolidate the past and stabilize brain ensembles (Buckner and Vincent, 2007). Moreover, the resting-state EEG can be viewed as starting point from which the cognition-associated neurophysiological activation starts to develop (Langer et al., 2012).

The prefrontal cortex was found to play a role in the maintenance of goal-related information, the integration of information to build new relations, and task context biases (Owen et al., 2005). These features are required in the present WM tasks. In the present study, WM training might have increased the efficiency of neural processing in the prefrontal cortex, resulting in decreased neurophysiological coherence. In addition to changes in the prefrontal cortex, WM studies frequently report concomitant activations in parietal regions (Owen et al., 1996; Jonides et al., 1993; Awh et al., 1996). Smith and Jonides suggested that the posterior parietal cortex is activated whenever short-term storage of verbal memory is required (Smith and Jonides, 1998). Moreover, the parietal cortex is involved in retaining temporal information and in reactivating relevant information (Ravizza et al., 2004), which is also essential to solve the WM tasks of the present study. The premotor cortex has been frequently observed as a neural correlate of WM processes in many studies (Owen et al., 1996; Jonides et al., 1993). On this basis, it has been suggested that activity in this region is related to the maintenance of visuospatial attention during WM tasks (Owen et al., 2005). However, the premotor cortex as well as the secondary sensory regions and the insular cortex could also be attributed to the common output demands of the reading and repetition demands of the task (Petersen et al., 1998). Although the insular cortex was positively correlated with WM in other WM studies (Engvig et al., 2010), the specific involvement in memory formation remains unclear.

The fronto-parietal network identified in the present study has been typically found by other research groups studying WM (Hampson et al., 2006; Jolles et al., 2013; Takeuchi et al., 2011). For example, Hampson et al. demonstrated in their fMRI connectivity analysis during WM performance a very similar connectivity pattern as the one revealed in our study (Hampson et al., 2006). In addition,
Sammer et al., using EEG and fMRI simultaneously during a mental arithmetic task, identified an EEG theta network comprising the same brain regions as in the present study (Sammer et al., 2007).

Further studies using graph-theoretical analysis on the basis of intracerebral activity could be improved by referring to the individual brain anatomy, which enables improved estimations for inverse modeling compared to an average brain by taking head size and cortical folding into account. In addition, one of the unsolved problems in connectivity analysis based on EEG data is the volume conduction, although to a lesser extent in the intracortical space than at sensor level. This problem is especially mitigated by using only the single centroid voxel of each ROI, as was done in the present study. Nevertheless, the analysis could even be improved by using lagged coherence, which, however, has not revealed any small-world topology in our preceding pilot study.

A recent study by Palva et al. (2010b) demonstrated that primarily networks in the alpha- and beta-frequency bands exhibit a memory-load dependent small-world structure during visual WM maintenance. Therefore, future studies investigating WM training effects should also investigate training-induced neurophysiological changes during WM task performance and should discriminate between encoding, retention and recall period.

To our knowledge, this is the first longitudinal study that has investigated the capacity of functional brain networks to adapt to changing demands by using graph-theoretical network analyses. To conclude, there were four main findings in the present study. (1) Theta oscillations power in the resting EEG is correlated with WM performance, and they could be increased by intensive WM training. (2) The better the WM performance, the more the functional networks in the theta band exhibit small-world topology. (3) Better WM performance was correlated with higher degree centrality of parietal cortical areas, and lower degree centrality of frontal areas. (4) WM training changed the network in the direction of network characteristics of high performers, with a shift of degree centrality from frontal to parietal areas, and a general increase of small-worldness.

Conflict of interest

No.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2013.01.008.

References


Ford JM, Mathalon DH, Whitfield S, Faustman WE, and Roth WT. Reduced communication between frontal and temporal lobes during talking in schizophrenia. Biological Psychiatry, 51: 485–492, 2002.


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