Attention modulates hemispheric differences in functional connectivity: evidence from MEG recordings

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The present study examined intrahemispheric functional connectivity during rest and dichotic listening in 8 male and 9 female healthy young adults measured with magnetoencephalography (MEG). Generalized synchronization within the separate hemispheres was estimated by means of the synchronization likelihood that is sensitive to linear as well as non-linear coupling of MEG signals. We found higher functional intrahemispheric connectivity of frontal and temporal areas within the right as compared to the left hemisphere in the lower and higher theta band during rest, and in the lower theta band during dichotic listening. In addition, higher synchronization in the lower theta band correlated with better task performance. In the upper alpha band, hemispheric differences in intrahemispheric connectivity of the frontal regions were found to be modulated by focused attention instructions. That is, attention to the right ear exaggerates the pattern of higher synchronization likelihood for the right frontal region, while attention to the left ear has an opposite effect. We found higher intrahemispheric connectivity in males compared to females as shown by higher synchronization in the lower alpha band. Taken together, our results reflect a physiological basis for functional hemispheric laterality and support the general assumption of sex differences in brain organization. Furthermore, in addition to studies that show that controlled attention processes modulate activation of the frontal areas, our study indicates that attention modulates ipsilateral functional connectivity in the frontal areas. This supports the idea of a supervisory role for the frontal cortex in attention processes.

Introduction

The two hemispheres of the human brain are known to be differentially involved in certain higher cognitive functions, a phenomenon known as functional hemispheric laterality. For example, in the great majority the left hemisphere is more strongly involved in language processing than the right hemisphere. Complementary to the idea that cognitive functions are localized to specific functionally specialized brain areas, the view that higher cognitive functions require integrated activity of multiple specialized neural systems gains increasingly support. The coordination of neural activity in several interconnected brain areas might be more important for cognitive functioning than the intrinsic properties of the separate brain areas in itself. Within the concept of functional hemispheric laterality, this notion might raise questions about the functional connectivity within the two hemispheres (intrahemispheric connectivity). Functional hemispheric differences may be determined through differences in functional coupling of areas within each separate hemisphere rather than through differences in the properties of the areas within the hemispheres per se.

During cognitive operations, particular brain regions become associated and activated in response to each other while other areas become dissociated. The pattern of this ‘dynamic’ functional connectivity will differ according to the particular cognitive operation. During cognitive operations that involve lateralized cerebral functions, connectivity patterns might differ for the left and right hemisphere. A cognitive task that can be used to examine hemispheric differences, specifically in language processing, is dichotic listening. Dichotic listening tasks involve simultaneous presentation of different auditory stimuli to the separate ears. Typically, verbal stimuli presented to the right ear (RE) are reported more accurately than verbal stimuli presented to the left ear (LE) (Kimura, 1967). This right ear advantage

(REA) is interpreted as reflecting left hemispheric specialization of language functions (Kimura, 1967). During dichotic listening, particular brain regions in the left hemisphere may become associated, while the corresponding regions in the right hemisphere, which is less involved in the task, may be not or less associated. The regions that are thought to be specifically involved in verbal dichotic listening tasks, are the temporal lobe regions mediating language processes, and the frontal lobe regions, which are known to play an important role in attention processes. Attention has been found to exert a strong influence on ear asymmetry in dichotic listening (Bryden, 1971; Bryden, Munhall, & Allard, 1983; Gootjes, Van Strien, & Bouma, 2004). In a study on elderly and Alzheimer's patients we found that reduced size of the corpus callosum, which is thought to mediate interhemispheric connectivity, affects ear asymmetry in healthy elderly (Gootjes, Bouma, Van Strien, Van Schijndel, Barkhof & Scheltens, 2005). Since left and right temporal and frontal regions are supposed to be differentially involved in dichotic listening, this might raise questions about the contribution of differences in intrahemispheric connectivity of the left and right hemispheres to ear asymmetry. Although hemispheric differences in functional connectivity might become specifically evident during cognitive processing that involves lateralized brain functions, differential connectivity within the separate hemispheres might be a stable factor that is apparent during rest as well. In a resting state intrahemispheric connectivity between spontaneously firing neurons might differentiate between the two hemispheres.

One mechanism by which brain areas may integrate their activity might be through the temporal correlation of neural activity (Varela, Lachaux, Rodriguez, & Martinerie, 2001). When large groups of neurons fire in synchrony, synchronous oscillations arise that can be examined by electro- and magneto-encephalography (EEG and MEG). It has been hypothesized that oscillations in different frequency bands are related to different cognitive functions. Changes in the theta band have been related to working memory (Klimesch, Schimke, & Schwaiger, 1994; Stam, van Walsum, & Micheloyannis, 2002b; Stam, 2000). Changes in the lower alpha band have been associated with attention processes, while changes in the upper alpha band have been associated with semantic memory (Klimesch, 1999; Klimesch, 1996). Depending on the cognitive operation that is involved, functional hemispheric asymmetries might become apparent in specific frequency bands. During dichotic listening, activity in both lower and upper alpha bands and lower and upper theta bands has been found to be differentially affected (Volf & Razumnikova, 1999).

Interactions between brain areas can be examined by investigating the similarity between two EEG or MEG signals recorded from different brain areas. Coherence analyses estimate the correlation between two EEG or MEG signals but they are only sensitive to linear properties of the signals and do not measure non-linear interactions between them. The role of non-linear coupling between brain regions has been emphasized by Friston (Friston, 2000a; Friston, 2000b; Friston, 2000c), who stresses the "labile" nature of normal brain dynamics. Optimal information processing in the brain would not be obtained by a static balance between specialization and integration, but rather by unstable, non-linear dynamics with rapidly fluctuating interactions (Friston, 2000b). Recently, new methods have been introduced to measure linear as well a non-linear coupling. These methods are based upon the concept of generalized synchronization (Rulkov, Sushchik, Tsimring, & Abarbanel, 1995). The synchronization likelihood proposed by Stam and Van Dijk (Stam & van Dijk, 2002a), is a new method to quantify generalized synchronization in dynamic biological systems like the brain: it detects statistically the intermittent existence of temporarily stable couplings over time. Recently, synchronous oscillations in MEG data have been proven to contain a significant non-linear component and synchronization likelihood has been demonstrated to measure this component (Stam, Breakspear, van Walsum, & van Dijk, 2003). Moreover, synchronization likelihood has been proven to be unaffected by changes in amplitude the signal (Stam and de Bruin, 2004). Being a useful method to explore linear and non-linear functional connectivity, synchronization likelihood can also be used to examine differences in intrahemispheric connectivity within the left and the right hemisphere. Appendix I contains a description of synchronization likelihood.

The present study was performed to examine intrahemispheric connectivity during rest and during a cognitive task that involves lateralized brain functions, namely dichotic listening. We used synchronization likelihood to investigate coupling of neural activity within the separate hemisphere as recorded with a whole head MEG system. Since attention is known to exert a strong influence on ear asymmetry in dichotic listening, we examined dichotic listening in three attention conditions, namely: passive listening, active listening with focused attention to the LE and active listening with focused attention to the RE. We hypothesized higher synchronization over the left, language-dominant, hemisphere, more specifically over the left temporal area, during all three dichotic listening conditions, due to strong involvement of the left hemisphere in the processing of the language-related stimuli in the dichotic task. Furthermore, we expect the frontal areas to show higher synchronization in the focused attention conditions compared to the passive listening condition due to increased involvement of attention processes that are supposed to be mediated by the frontal areas (Duncan & Owen, 2000). Since it is generally assumed that females tend to have a less lateralised brain organization than males (Shaywitz et al., 1995; Voyer, Voyer, & Bryden, 1995), and gender dependent changes in coherence have been described in EEG studies (Volf et al., 1999), we also examined sex differences in synchronization.

Materials and methods

Participants

Seventeen participants (8 men, 9 women) with ages ranging from 19-30 years (mean age ± SD was 23.7 ± 3.2 years) were recruited among students from the *Vrije Universiteit* in Amsterdam. Informed consent was obtained from all participants. Hand preference was evaluated with a 10-item Dutch handedness questionnaire (van Strien, 1992). All participants were native Dutch speakers and had a minimum score of +9 on a scale ranging from -10 (strongly left-handed) to +10 (strongly right-handed). Auditory screening was used to examine hearing threshold at 1000, 1500, 2000, 3000 and 4000 Hz and revealed normal hearing in all participants. Individuals with more than 5 dB difference between hearing thresholds of the RE and LE were excluded from participation. Participants reported no presence of hearing problems, speech therapy, neurological disorders or psychiatric disorders.

Dichotic listening

Ten monosyllabic Dutch digits (1-6, 8, and 10-12) were spoken by a female voice and were digitally recorded. The duration of each digit was digitally equated to 450 ms. Digits were arranged in pairs in such a way that two consecutive digits in a pair were not allowed. The two digits in each pair were presented simultaneously: one at the RE and one at the LE. Each trial consisted of four pairs (eight different digits) in sequence in such manner that two consecutive digits were not allowed to follow after each other in one ear. The interval between pairs within a trial was 50 ms and the inter-trial interval was 9.5 s (Fig. 1). All digit combinations were counterbalanced between the two channels within the test trials of each condition. Auditory stimuli were delivered to both ears using EARTone 3A Insert Earphones (Cabot Safety Corporation, Indianapolis, USA). Sound was delivered through 110 cm long plastic tubing and a plastic ear tip at a mean sound pressure level of 85 dB. All participants confirmed that this level was audible and comfortable. The dichotic listening task consisted of 3 conditions: a passive listening (PA) condition, a focused attention condition in which attention had to be focused to the LE (ATT-LE) and a focused attention condition in which attention had to be focused to the RE (ATT-RE). Each condition was composed of five warm-up trials and 50 test trials. In the ATT-LE and ATT-RE condition, participants had to recall first as many digits as possible from the ear they had to attend to and then as many digits as possible from the other ear. Percentage recall performance in the ATT-LE and ATT-RE condition was calculated by dividing the total number of correctly recalled digits (separately for the LE and RE) by 200 (maximum score per ear) and multiplying it with 100. In addition, ear asymmetry was examined by calculating a laterality quotient according to the following formula: LQ = (attended ear – unattended ear) / (attended ear + unattended ear). To keep possible influences of preparing and giving a verbal response similar between conditions, in the PA condition, the participants had to indicate verbally the end of each dichotic trial by saying ‘yes’. All participants started with the PA condition, followed by the two focused attention conditions. The order of the ATT-LE condition and the ATT-RE condition was counterbalanced across age and gender group.

MEG

Neuromagnetic fields were recorded in a magnetically shielded room (Vacuum-schmelze GmbH, Germany) using a 151- channel whole-head MEG system (CTF Systems Inc., Canada) during a no-task, eyes-closed (EC) condition followed by 3 dichotic listening conditions. The signals were bandpass filtered at 0.25 to 125 Hz and digitized at 250 Hz. For each condition, eight artefact free epochs of 2 s MEG data were combined to one epoch of around 16 s (4096 samples) that was used for further analysis. For the dichotic listening conditions, these epochs coincided exactly with auditory presentation of the dichotic stimuli. Separate analyses were performed on data filtered in the following frequency bands: 4-6 Hz (lower theta), 6-8 Hz (upper theta), 8-10 Hz (lower alpha) and 10-12 Hz (upper alpha). The choice of these bands was based on the fact that theta and alpha bands have been described to be differentially affected during dichotic listening (Volf et al, 1999).

Synchronization likelihood

The synchronization likelihood, proposed by Stam and Van Dijk (Stam et al., 2002a), is a method that yields the degree of synchronization or coupling between equal-length time series. The measure is based upon the concept of generalized synchronization as introduced by Rulkov et al. (Rulkov et al., 1995). General synchronization is said to exists between two dynamical systems X and Y if a continuous one-to-one function F exists such that the state of one of the systems (the response system) is mapped onto the state of the other system (the driver system): Y = F(X) (Rulkov et al., 1995). F may be any function, linear or nonlinear, as long as it is locally smooth; therefore this definition of synchronization is much more general than the linear correlation assessed with coherence analysis. This means that general synchronization exists between two systems X and Y if the following holds: if X is in the same state at two different times (e.g. t2, t6 and, t9, see Table 1), Y will also be in the same state at these times. The state of system X and system Y need not resemble each other at these times. In contrast to coherence, synchronization likelihood measures linear as well as non-linear interdependencies and it can do so as a function of time, making it suitable for non-stationary time series. Generally said, synchronization likelihood can statistically detect the alternating existence of temporarily but stable coupling over time, which makes it very suitable to examine brain dynamics. In Appendix I a description of synchronization likelihood can be found. In the present study, we calculated synchronization likelihood between all possible MEG channel pairs within the separate hemispheres. Subsequently, for each channel, we averaged the synchronization likelihood between that channel and all ipsilateral channels to obtain one averaged synchronization likelihood value per channel. Next, we grouped MEG channels in five areas according their location above the hemispheres and averaged the synchronization likelihood within each group to obtain for each hemisphere five overall synchronization likelihood values for respectively central, frontal, occipital, parietal and temporal located channels. These overall synchronization likelihood values represent the mean synchronization of the signals of one selective area with the signals of the whole ipsilateral hemisphere.

Statistical analysis

To examine recall performance, analysis of variance (ANOVA) with repeated measures was done with Ear (LE and RE) and Condition (ATT-LE and ATT-RE) as within-subject variables and Gender (male and female) as between-subject variables. To examine ear asymmetry, ANOVA with repeated measures was done with Condition (ATT-LE and ATT-RE) as within-subject variables and Gender (male and female) as between-subject variables.

For each frequency band, synchronization likelihood was analyzed separately for the EC condition and the dichotic listening conditions with repeated measures ANOVAs using Huyn-Feldt corrected p-values to correct for possible violations against the sphericity assumption in a repeated measures design. Analyses of data of the EC condition were done with Hemisphere (LH and RH) and Area (central, frontal, occipital, parietal and temporal) as within-subject variables and Gender (male and female) as between-subject variable. Analyses of synchronization likelihood in the dichotic listening conditions involved an additional within-subject variable, namely Condition (PL, ATT-RE and ATT-LE). Correlations between synchronization likelihood and total recall performance, RE and LE recall performance, and

LQ with were examined with partial correlation coefficients correcting for gender. For all statistical analyses a significance level of .05 was employed.

Results

Dichotic listening

ANOVA yielded a significant main effect for Ear, F(1, 14)=11.42, p<.01, reflecting better recall performance for the RE. A significant interaction for Ear x Condition, F(1, 14)=160.05, p<.001, indicated that performance of the attended ear was better than for the unattended ear and that this difference was larger in the ATT-RE-condition (Fig. 2). LQ scores were higher in the ATT-RE condition (M=.42, SEM=.05) compared to the ATT-LE condition (M=.29, SEM=.04), as reflected by a significant main effect for Condition, F(1, 14)=15.13, p<.01 (Fig. 2). No gender effects were found.

Synchronization likelihood

Eyes-closed condition (EC)

In the lower (4-6 Hz) and upper (6-8 Hz) theta band, we found in addition to an Area effect (F(4, 60)=11.87, p<.001 and F(4, 60)=22.81, p<.001, respectively) a significant overall Hemisphere x Area effect (F(4, 60)=3.16, p<.05 and F(4, 60)=3.05, p<.05, respectively). Synchronization likelihood for the frontal and temporal areas, but not for the other areas, was significantly higher within the right compared to the left hemisphere (Fig. 3B and 3C). In the lower alpha band (8-10 Hz), in addition to an Area effect, F(4, 60)=23.30, p<.001 and a Gender effect, F(1, 15)=27.75, p<.001, we found a significant Area x Gender effect, F(4, 60)=5.17, p<.01. Synchronization likelihood values were significantly higher for the men compared to the women for central, parietal, temporal, and occipital areas, while the difference in synchronization likelihood values between males and females approached significance for the frontal area (Fig. 4A). In the upper alpha band (10-12 Hz), we found an Area effect, F(4, 60)=17.92, p<.001.

Dichotic listening conditions (PL, ATT-RE, and ATT-LE)

In the lower theta band (4-6 Hz), we found in addition to an Area effect, F(4, 60)=28.78, p<.001, a significant Hemisphere x Area effect, F(4, 60)=28.78, p<.001, indicating higher synchronization likelihood for the right frontal and temporal areas compared to the same areas within the left hemisphere (Fig. 3A). In the upper theta band (6-8 Hz), a main effect for Area was significant, F(4, 60)=30.88, p<.001. In the lower alpha band (8-10 Hz), in addition to an Area effect, F(4, 60)=21.62, p<.001, a significant overall Area x Gender effect, F(4, 60)=2.80, p<.05 was found. Synchronization likelihood values were significantly higher for the men compared to the women in the temporal area in the dichotic listening condition (Fig. 4B). Additionally, a Condition x Gender effect for the parietal region was significant, F(2, 30)=3.878, p<.05. In the ATT-RE and PA condition, we found higher synchronization likelihood in the men compared to the women. However, in the ATT-LE condition, synchronization likelihood was equal for both gender groups (Fig. 4C). In the upper alpha band (10-12 Hz), in addition to an Area effect, F(4, 60)=21.84, p<.001, a significant Condition x Hemisphere x Area effect, F(8, 120)=2.4, p<.05 was found. In the ATT-RE condition, we found larger asymmetry of synchronization likelihood values for the left and right frontal area than in the PA condition, while in the ATT-LE condition, we did not find hemispheric asymmetry in synchronization likelihood for these areas (Fig. 5).

Correlation between dichotic listening and synchronization likelihood

In the lower theta band (4-6 Hz), recall performance of the unattended RE and total recall performance in ATT-LE condition were correlated with synchronization likelihood for the right frontal area (r= .64, p<.01, and r = .74, p<.01, respectively) (Fig. 6). Additionally, LQ in ATT-LE condition was correlated with synchronization likelihood for the left frontal and left parietal area (r= .69, p<.01, and r = .56, p<.05, respectively).

Discussion

In the present study, we examined intrahemispheric connectivity during rest and dichotic listening by looking at the generalized synchronization of neural activity of various brain areas within the separate hemispheres. The major findings can be summarized as follows.

1. We found hemispheric differences in intrahemispheric synchronization likelihood in the lower and upper theta band for the frontal and temporal regions indicating higher intrahemispheric functional connectivity of these brain areas in the right hemisphere.
2. Synchronization in the lower theta band correlated with dichotic task performance. Higher synchronization in this band was associated with better total performance and better unattended RE performance in the right frontal area, and with higher ear asymmetry scores in the left frontal and left parietal areas.
3. In the upper alpha band, we found a differential effect of focused attention instructions on hemispheric differences in synchronization likelihood for the frontal regions. When attending to the RE, the differences in synchronization between the right and left frontal regions increased, while it decreased when attention had to be focused to the LE.
4. In the lower alpha band, we found a gender effect as reflected by higher synchronization likelihood, and thus increased intrahemispheric functional connectivity, in men compared to women.

In the EC condition, we found higher synchronization in the lower and upper theta band for the right frontal and right temporal areas compared to the corresponding areas in the left hemisphere (Fig. 3B and 3C). In the dichotic listening condition, synchronization was higher for the right frontal and right temporal areas in the lower theta band (Fig. 3A), but not in the upper theta band. Although performance on the dichotic listening task relies strongly on language functions that are thought to be mediated mainly by the left hemisphere, this does not result in increased functional connectivity over the left compared to the right hemisphere during the task. Higher synchronization likelihood over the right frontal and right temporal areas points to increased ipsilateral connectivity of the right hemisphere and seems to be a stable and intrinsic property of this hemisphere rather than a task-specific effect. Increased connectivity within the right hemisphere has been found in studies on EEG coherence as well (Koeda et al., 1995; Beaumont & Rugg, 1979; Tucker, Roth, & Bair, 1986). A hemisphere effect, specifically in the theta band, has been found in a combined group of control subjects and siblings of schizophrenics, but unfortunately the authors did not report the direction of the asymmetry (Mann, Maier, Franke, Roschke, & Gansicke, 1997). Furthermore, also an imaging study using PET, that measures metabolic correlation between brain regions, showed increased coupling of ipsilateral cortical areas in the right compared to the left hemisphere during rest (Kang et al., 2003). In addition, diffusion tensor maps indicate greater alignment of white matter fiber tracts in the right hemisphere (Peled, Gudbjartsson, Westin, Kikinis, & Jolesz, 1998). However, to our knowledge, the present study is the first that found increased connectivity within the right hemisphere with non-linear analyses of MEG signals.

Within the field of neuropsychology, the left hemisphere is traditionally regarded to be more focally organized, involving local networks within specific cortical regions, while the right hemisphere is regarded to be more globally organized, involving diffuse networks that interconnect regions with the whole ipsilateral hemisphere (Semmes, 1968). Moreover, the right hemisphere has been found to be more strongly involved than the left in arousal and attention processes which are processes that are supposed to be more globally organized as well (Posner, 1994). Our measure of intrahemispheric connectivity involves a rather global measure; since it estimates the coupling of specific brain regions with the whole ipsilateral hemisphere, it measures the function of diffuse networks within the separate hemispheres rather than that of more local intrahemispheric networks.

Higher intrahemispheric synchronization within the right hemisphere was specific for both theta bands during rest and for the lower theta band during dichotic listening. Theta band synchronization has been hypothesized to be specifically related to working memory (Klimesch et al., 1994; Stam, 2000; Stam et al., 2002b; Stam, 2000; Stam et al., 2002b). Furthermore, theta band synchronization, specifically in large-range networks, has been found to relate to performance on an intelligence task (Anokhin, Lutzenberger, & Birbaumer, 1999). Also in the present study, task performance was related to theta activity. Better total performance and better unattended RE performance was associated with increased lower theta band synchronization for the right frontal area in the ATT-LE condition. The frontal areas are assumed to be strongly involved in working memory (Duncan et al., 2000). The total number of recalled digits and more specifically the number of recalled digits from the unattended RE, might be an indication of working memory capacity: the better the working memory, the more digits from the unattended ear are reported, that is, after recall of the digits from the attended ear. Theta synchronization of the right frontal area might thus indicate working memory in dichotic listening. Furthermore, increased ear asymmetry in the ATT-LE condition was associated with increased lower theta band synchronization for the left frontal and left parietal areas. This association might indicate that increased connectivity for the left hemisphere results in a better distinction between stimuli presented to the dominant and non-dominant ear when attention has to be focused to the non-dominant LE.

It is interesting to note that the presence of an association of recall performance and ear asymmetry with theta band synchronization is only apparent in the ATT-LE condition. The difference between focusing attention to the LE or to the RE in dichotic listening has been pointed out earlier (Hugdahl, 2000; Hugdahl et al., 2003). Without focused attention instructions, (bottom-up) processing of verbal stimuli would rely strongly on hemispheric differences in language processing, which normally results in superior performance of the (dominant) RE. Focused attention instructions increase top-down processing of the stimuli. However, only when attention has to be focused to the (non-dominant) LE, top-down and bottom-up processing have opposite effects. Therefore, dichotic performance in the ATT-LE condition puts stronger demands on the ability to suppress irrelevant information processing than in the ATT-RE condition. Such inhibitory executive functions are assumed to be mediated by the frontal areas. Also, the parietal regions have been hypothesized to be involved in attention, specifically in "disengagement operation" (when attention has to move from one location to another in the contralateral field) (Posner, Walker, Friedrich, & Rafal, 1984). Moreover, hemispheric asymmetries in parietal cortex have been found to indicate increased involvement of left compared to right parietal cortex to during voluntary shifts of spatial attention (Wilson, Woldorff, & Mangun, 2005). Our finding of an association of recall performance and ear asymmetry with synchronization likelihood for the left and right frontal and left parietal areas only in the ATT-LE condition, might indicate that intrahemispheric communication of specifically these areas plays an important role in ear asymmetry when increased top-down processing is involved.

A modulating effect of top-down processing on synchronization has been found earlier in animal studies (Fries, Reynolds, Rorie, & Desimone, 2001; von Stein, Chiang, & Konig, 2000). Top-down processing is suggested to be mediated by interactions specifically in the middle-frequency ranges (4-12 Hz) (von Stein et al., 2000; von Stein & Sarnthein, 2000). The present study underscores this notion. In the upper alpha band, hemispheric differences in synchronization likelihood were found to vary between focused attention conditions (Fig. 5). Attention to the RE exaggerates the pattern of higher synchronization likelihood for the right frontal region, apparent in the PA condition. Attention to the LE on the other hand, has an opposite effect: it diminishes the hemispheric differences in frontal connectivity, probably by increasing functional connectivity of the left frontal areas. Increased involvement of top-down processing in the ATT-LE condition might be associated with this finding. In addition to studies that show that controlled attention processes modulate activation of the frontal areas in dichotic listening (Thomsen, Rimol, Ersland, & Hugdahl, 2004a; Thomsen et al., 2004b), our results suggest that top-down attention processes modulate ipsilateral functional connectivity between the frontal areas and the ipsilateral hemisphere. Connectivity of the prefrontal cortex with other brain regions has been proposed as the basis of cognitive control (Miller, 1999; Miller, 2000). Moreover, attention to a motor task has been found to increase effective connectivity between prefrontal and premotor cortex as measured with fMRI (Rowe, Friston, Frackowiak, & Passingham, 2002). Our finding that functional connectivity of the frontal areas is modulated by focusing attention, supports the idea of a supervisory role for the frontal cortex in attention processes.

In the lower alpha band (8-10 Hz), we found sex differences revealing higher synchronization for males both in the EC and dichotic listening conditions (Fig. 4A and 4B). This suggests that the ipsilateral cortical areas are more strongly connected in the male brain than in the female brain. Sex differences have been found in complexity measures of EEG signals as well. Complexity measures estimate the relative number of independently oscillating neural cell assemblies that contribute to the (local) EEG signal; increased complexity indicates decreased coupling between (local) neural cell assemblies. It has been reported that females have higher complexity measures in the theta (4-7 Hz) and lower alpha (8-10 Hz) band in rest and during a working memory task (Stam, 2000), which points at decreased local connectivity. In contrast to decreased intrahemispheric connectivity in females, EEG studies on interhemispheric connectivity using linear coherence measures found increased connectivity between the contralateral hemispheres in females during photic stimulation (Wada et al., 1996), and during cognitive tasks (Beaumont et al., 1979). Decreased intrahemispheric connectivity in females, as found in the present study, might be strongly related to increased interhemispheric connectivity in that sense that decreased intrahemispheric connectivity might put stronger demands on interhemispheric communication. This notion fits nicely in the general assumption that the functional organization of the brain is less lateralised in females than in males (Voyer et al., 1995). The constant ongoing information processing in the brain, not only during cognitive operations but also during rest, might involve more local activation patterns in the male brain, while in the female brain, more global activation patterns across the hemispheres are involved. Synchronization likelihood is also most suitable to examine interhemispheric connectivity, future studies at the level of interhemispheric connectivity might shed more light on this issue.

Although we did not find any sex difference in performance on the dichotic listening task, we did find a differential effect of the focused attention instructions on synchronization likelihood for the parietal areas in males and females in the lower alpha band. Again, this underscores the important role of the parietal areas in attention (Behrmann, Geng, & Shomstein, 2004; Ghatan, Hsieh, Petersson, Stone-Elander, & Ingvar, 1998). In the ATT-RE and PA condition, we found higher synchronization likelihood in the male participants compared to the females. However, in the ATT-LE condition, synchronization likelihood was equal for both gender groups (Fig. 4C). Although females and males have similar performance level, the focused attention instructions evoke different connectivity patterns across the genders. Gender dependent changes in EEG coherence in the lower alpha band in dichotic listening compared to rest have been found earlier (Volf et al., 1999). Females were found to show greater increase of rest to task coherence than males, but in this study no focused attention conditions were included. Also during a mental rotation task gender dependent EEG changes in the lower alpha band were found (Rescher & Rappelsberger, 1999). Males were found to show higher intrahemispheric coherence in the lower alpha band compared to females. In line with our finding of a differential effect of focused attention instructions, the direction of gender related changes seems to be strongly task related. Next to the gender differences that we found during rest, this underlines the idea of differential brain organization in the male and female brain.

Research has indicated that oscillations in different frequency bands are related to different cognitive functions (e.g. Klimesch, 1999; Basar, Basar-Erglu, Karakas, & Schurmann, 2001). The appropriate selection of frequency bands is a critical issue in this context. Narrow-band filtering is common practice in EEG studies and it has been found that bandwidths that are narrow as 2 Hz, can respond selectively to specific cognitive functions. For example, the upper alpha band, determined as a band of 2 Hz above the individual alpha frequency, is found to respond selectively to semantic memory demands and to behave in a completely different way compared to the lower alpha band (Klimesch, 1999). Moreover, the use of narrow frequency bands reduces the danger that frequency specific effects go undetected or cancel each other out. In the present study synchronization likelihood was calculated in both lower and upper alpha and in lower and upper theta bands. Our results indicate frequency specific effects: gender effects were found specifically in the lower alpha band, dichotic listening performance was related specifically to the lower theta band, while effects of attention instructions appeared specifically in the higher alpha band.

Taken together, our results reflect a physiological basis for functional hemispheric laterality and support the general assumption of sex differences in cerebral lateralization. Hemispheric differences in functional connectivity do not only depend upon cognitive or sensory brain functioning but can be found during rest as well. It addition to studies that show that voluntary attention processes modulate activation of the frontal areas, our study indicates that attention also modulates functional connectivity of the frontal areas within the hemisphere. This supports the idea of a supervisory role for the frontal cortex in attention processes.

Appendix I

The following description of synchronization likelihood is based on Stam and Van Dijk (2002a) and taken from Stam et al. (2003). To make the concept of synchronization likelihood operational, we need some concept of the state of a system, and a metric for the similarity of two states. This can be achieved by using the framework of non-linear dynamical systems theory and state space embedding (a very accessible introduction can be found in Pritchard and Duke (1995); a more recent but rather technical review is Schreiber (1999).

We assume time series of measurements x_i and y_i ($i = 1, \ldots, N$) recorded from X and Y. From these time series, we reconstruct vectors in the state space of X and Y (these vectors correspond to the "states" of both systems) with the method of time-delay embedding (Takens, 1981).

$$Xi = (X_i, X_{i+l}, X_{i+2l}, \ldots, X_{i+(m-1)l}) \qquad (1)$$

Here l is the time lag and m the embedding dimension. In a similar way vectors Y_i are reconstructed from the time series y_i. Now if the state of Y is a function of the state of X, each X_i will be associated with a unique Y_i. Also if two vectors X_i and X_j are almost identical (the distance between X_i and Y_i is very small) then, because of the continuity of F, Y_i and Y_j will also be almost identical. Thus, the distance between two vectors in a state space is metric of their similarity. We now have the required concepts of "state" and "similarity between states" and can continue to define a measure of synchronization in terms of these concepts.

The synchronization likelihood expresses the chance that if the distance between X_i and X_j is very small, the distance between Y_i and Y_j will also be very small. For this, we need a small critical distance ε_x, such that when the distance between X_i and X_j is smaller than ε_x, X will be considered to be in the same state at times i and j. ε_x is chosen such that the likelihood of two randomly chosen vectors from X (or Y) will be closer than ε_x (or ε_y) equals a small fixed number p_{ref}. It is important to note that p_{ref} is the same for X and Y, but ε_x need not be equal to ε_y. (Please not that p_{ref} has nothing to do with a significance level; it is simply a way to control the value of S in the case no synchronization between the two systems exists.) Now the synchronization likelihood S between and Y at time i is defined as follows:

$$S_i = \frac{1}{N} \sum_j \vartheta(\varepsilon_y - | Y_i - Y_j |) \mathrm{if}(| X_i - X_j | < \varepsilon_x) \tag{2}$$

Here we only sum over those j satisfying w1 < |i-j| < w2, and X_i - X_j < ε_x. N is number of j fulfilling these conditions. The value of w1 is the Theiler correction for autocorrelation and w2 is used to create a window (w1 < w2 < N) to sharpen the time resolution of S_i (Theiler, 1986). When no synchronization exists between X and Y, S_i will be equal to the likelihood that random vectors Y_i and Y_j are closer than ε_y; thus $S_i = p_{ref}$. In case of complete synchronization $S_i = 1$ Intermediate coupling is reflected by $p_{ref} < S_i < 1$. Because p_{ref} is the same for X and Y, the synchronization likelihood is the same considering either X or Y as the driver system. Choosing p_{ref} the same for X and Y is necessary to ensure that the synchronization likelihood is not biased by the degrees of freedom or dimension of either X or Y (Stam et al., 2002a).

From the basic definition of S_i as given in equation (2), we can derive several variations of averaging over time, space or both. First we can consider the average synchronization likelihood between X and two or more systems. If we denote the index channel by k, S_{ki} is the average synchronization between channel k and all other channels at time i. By averaging over all time points i, we obtain S_k. Averaging over all channels k gives S, the overall level of synchronization in a multi channel epoch.

In the present study, synchronization likelihood was computed with the following parameter settings: l = 10; m = 10, w1 = 100 (product of lag and embedding dimension); w2 = 400; p_{ref} = 0.05. The length of w1 and w2 is expressed in samples. There is no unique way to choose these parameters; however, the present parameter choices proved to be effective in distinguishing between experimental conditions in working memory task (Stam et al, 2002a) and between MEG recordings of healthy controls and Alzheimer patients (Stam et al, 2002b)

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Fig. 1. Schematic representation of dichotic stimuli and task over time

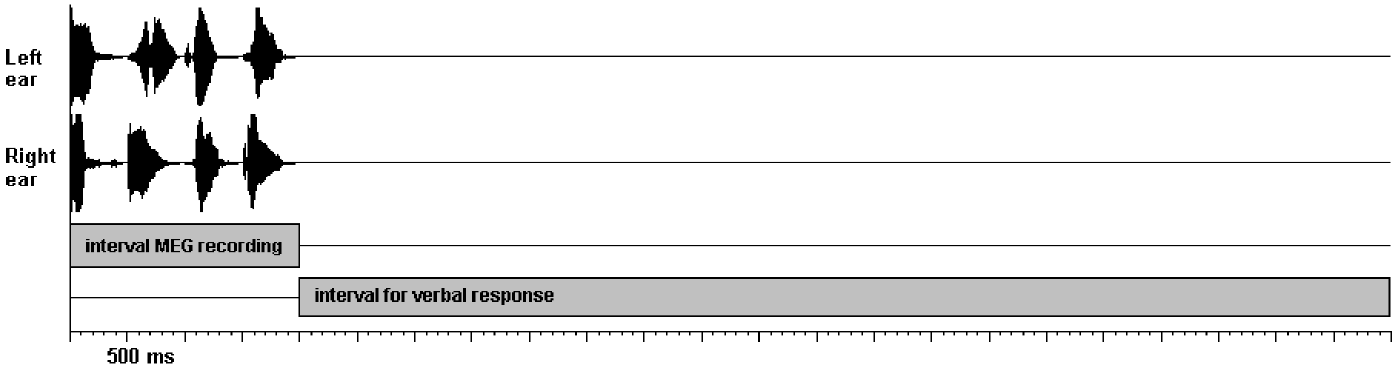

Fig. 2. Mean (+/- SEM) recall performance in the dichotic listening task in the two focused attention (ATT) conditions. LE, left ear; RE, right ear

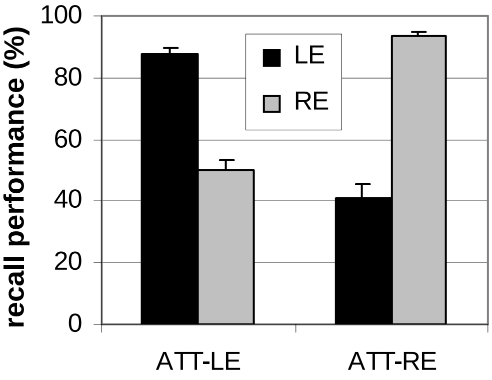

Fig. 3. Mean (+/- SEM) synchronization likelihood per area and hemisphere during the eyes closed (EC) condition in the lower (4-6 Hz) (A) and upper theta (6-8 Hz) (B) band and during dichotic listening in the lower theta band (4-6 Hz) (C). C = central, F = frontal, O = occipital, P = parietal, T = temporal, L = left hemisphere, R = right hemisphere

Note that synchronization likelihood was significantly higher within the right hemisphere compared to the left hemisphere for the frontal and temporal areas, but not for the other areas.

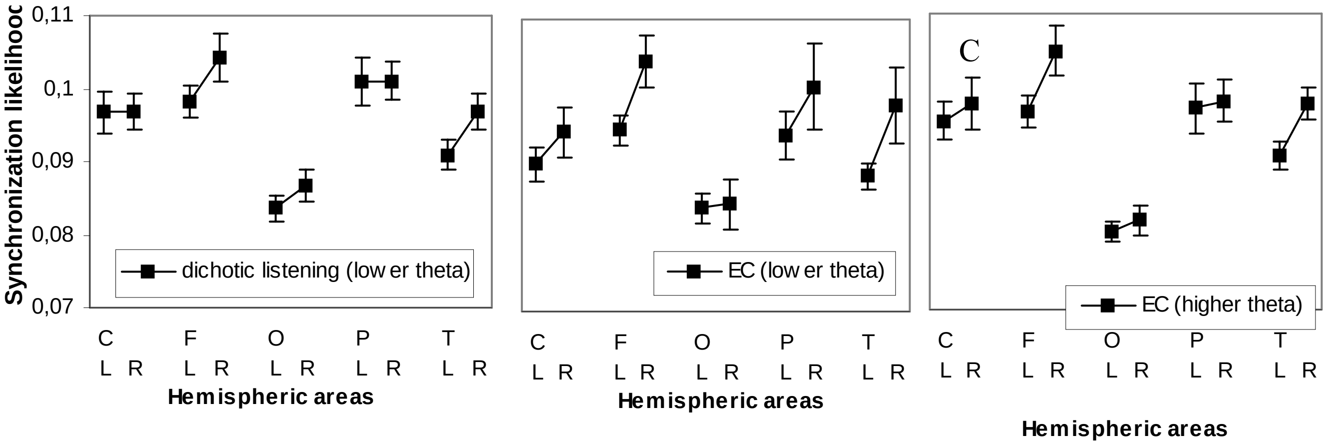

Fig. 4. Mean (+/- SEM) synchronization likelihood per areas and gender in the eyes closed (EC) (A) and dichotic listening conditions (B and C) in the lower (8-10 Hz) alpha band. C = central, F = frontal, O = occipital, P = parietal, T = temporal, M = male, F = female

Figure A shows that synchronization likelihood in the EC condition is higher in male than in female for all except the frontal areas. Note in figure B that synchronization likelihood in the dichotic listening condition is higher in male than in female only for the temporal areas. Figure C illustrates that synchronization likelihood in the ATT-RE and PA condition is higher in male than in female for the parietal areas, while in the ATT-LE.

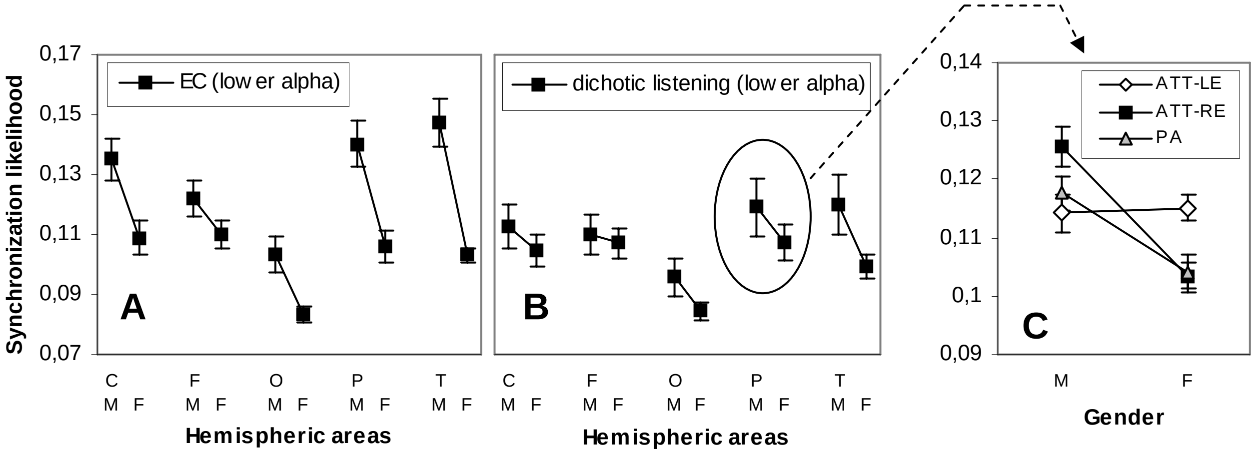

Fig. 5. Mean synchronization likelihood per area and hemisphere during the dichotic listening conditions in the upper (10-12 Hz) alpha band (for illustrative reasons, SEM are not depicted). C = central, F = frontal, O = occipital, P = parietal, T = temporal, L = left hemisphere, R = right hemisphere

Note that, compared to the PA condition, the asymmetry of synchronization likelihood in the left and right frontal areas is increased in the ATT-RE condition and decreased in the ATT-LE condition.

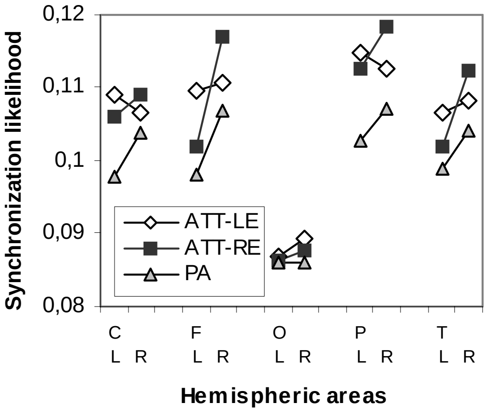

Fig. 6. Scatter plot of recall performance of the unattended RE (maximum score is 200) and synchronization likelihood for the right frontal areas in the ATT-LE condition.

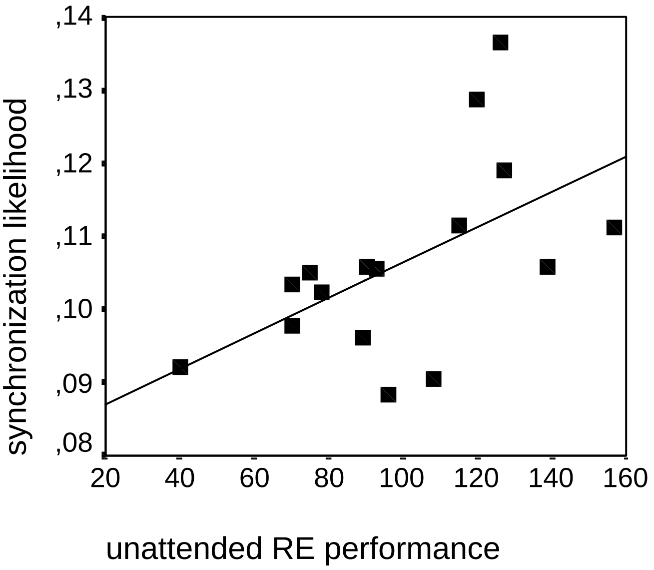

Table 1. Concept of generalized synchronization: at each time point that system X is in state A (at time 2, 6 and 9), system Y is in state B. (N.B.: for illustrative reasons, alphabetic symbols are used to represent the specific state of the systems at a certain time-point, however it should be stressed that the states as well as the relationship between the states can vary along a continuous scale.)

Time	1	2	3	4	5	6	7	8	9	10
State of system X	D	A	G	H	Z	A	B	T	A	Z
State of system Y	E	B	C	R	P	B	H	S	B	P