Abnormal slow wave mapping (ASWAM)—A tool for the investigation of abnormal slow wave activity in the human brain

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Abstract

Slow waves in the delta and theta frequency range, normal signs of deactivated networks in sleep stages, are considered ‘abnormal’ when prominent in the waking state and when generated in circumscribed brain areas. Structural cortical lesions, e.g. related to stroke, tumors, or scars, generate focal electric and magnetic slow wave activity in the penumbra. Focal concentrations of slow wave activity exceeding those of healthy subjects have also been found in individuals suffering from psychiatric disorders without obvious structural brain damage. Hence, identification and mapping of abnormal slow wave activity might contribute to the investigation of cortical indications of psychopathology.

Here I propose a method for abnormal slow wave mapping (ASWAM), based on a 5 min resting magnetoencephalogram (MEG) and equivalent current dipole fitting to sources in the 1–4 Hz frequency band (delta) in anatomically defined cortical regions. The method was tested in a sample of 116 healthy subjects (59 males), with the aim to provide a basis for later comparison with patient samples. As to be expected, delta dipole density was low in healthy subjects. However, its distribution differed between genders with fronto-central > posterior dipole density in male and posterior dominance in female participants, which was not significantly related to either age or headsize. Results suggest that this method allows the identification of ASWA, so that comparison against Z-scores from a larger normal control group might assist diagnostic purposes in patient groups. As specific distributions seem to reflect differences between genders, this should be considered also in the analysis of patient samples.

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1. Introduction

Slow wave rhythms are a normal correlate of sleep stages, whereas in the waking state they are found in a variety of developmental and degenerative disorders, in toxic and metabolic encephalopathy and in other neurological conditions. If the neural generators are focally concentrated, slow wave rhythms appear in the vicinity of a structural lesion, that is, focal electromagnetic slow waves are generated in the surround of circumscribed lesions or neuronal tissue otherwise affected by pathology such as cerebral infarct, contusion, local infection, tumor, epileptic foci and subdural hematoma (Baayen et al., 2003; de Jongh et al., 2001a,b, 2002, 2003; Gallen et al., 1992, 1993; Tanaka et al., 1998; Vieth et al., 1998, 1996, 2001; Walter, 1936). Furthermore, reduced levels of neurotransmitters (e.g. acetylcholine) can lead to an increase of delta activity (Neufeld

et al., 1994; Osipova et al., 2003; Riekkinen et al., 1990, 1991), consequently slowing of EEG is well known in Alzheimer’s disease and cholinergic atrophy is believed to play an important role. Consequently, cholinergic monoaminergic blockade can partially reverse EEG slowing and (Dringenberg, 2000). Varying with changes in metabolism and blood flow consequent upon the insult (Meinzer et al., 2004; Strik et al., 2002; Vieth et al., 2001), abnormal slow wave activity has been attributed to a ‘dysfunctional state’ of the neuronal tissue (Lewine and Orrison, 1995). We may assume that ‘de-afferented’ neural networks cut off from major input sources produce focally generated slow waves.

In addition to neurological disease abnormal slow waves are observed in psychopathological conditions (Canive et al., 1996; Fehr et al., 2001, 2003; Fernandez et al., 2003; Wienbruch et al., 2003). Using a single equivalent current dipole model with band pass-filtered data in the delta (1.5–4 Hz) and theta (4–8 Hz) ranges, we (Fehr et al., 2003; Fernandez et al., 2002; Wienbruch et al., 2003) determined the origin of focal slow waves and a density function of focal generators. In psychiatric patients these density functions were circumscribed to regions generat-

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ing large-amplitude slow waves. Moreover, the localization of these foci distinguished diagnostic groups, with schizophrenia patients exhibiting more slow waves in association cortex, patients with Alzheimer's dementia being characterized by parietal foci (Fernandez et al., 2002), whereas a suppression of frontal activity compared to any of the comparison groups characterized depressive patients (Wienbruch et al., 2003). Given that the group-specific pattern of slow wave activity was not strongly affected by mental activation (Fehr et al., 2003), focal slow wave activity was assumed to indicate dysfunctions related to neuronal network communication caused by the psychological disorder. Thus, the mapping of abnormal brain oscillations might help to understand critical brain mechanisms in these disorders, and thereby support diagnosis as well as psychological and biological treatment development.

However, the benefit of abnormal slow wave mapping (ASWAM) in the study of 'dysfunctional' cortical network communication in clinical studies relies on testing of the method in healthy subjects. Here, we propose an improved method for ASWAM, extended from an initial method (Wienbruch et al., 2003) to allow Z-score based analysis of single subjects and group results of dipole density on both a voxel-scale and a scale of defined brain regions. The slow wave pattern determined from spontaneous magnetoencephalography (MEG) under resting conditions in a larger sample of healthy subjects should document the range of normal slow wave distribution and the potential variation with age and gender as a basis for the comparison with clinical groups. With this aim the present paper concentrates on the description of the method of ASWAM and its assessment in a sample of 116 healthy subjects, while further evaluation of the power of this method to distinguish between groups will be presented elsewhere.

MEG seems advantageous for the identification of focal slow wave activity as it allows the separation of focally generated slow waves from those with widespread sources, which is not the case with EEG. The same brain processes are differentially imaged by MEG and EEG and combined measurements of both MEG and EEG quantitatively illustrate this point (Eulitz et al., 1997). From a theoretical point of view, this may result from the nature of each signal. That is to say, EEG is strongly affected by the properties acting on the extracellular volume currents (e.g. conductivity) triggered mainly by postsynaptic potentials whereas MEG is thought to arise from the intracellular branch of this process, i.e., from the currents that flow from the dendrite to the soma. In a spherical volume conductor model MEG is only sensitive to currents flowing tangentially to the surface of the sphere. This is still (mainly) valid for realistic volume conductor models even if radial sources' contributions to the magnetic fields outside the volume conductor amounts to a degree of about 10%. Widespread sources that extend across both sides of a sulcus have a strong radial contribution. However, as the activity in opposing walls of the sulci partially cancel each other, a weak tangential dipole source remains. Consequently, for focal sources located in sulci (which comprise two-third of the cortex) the signal-to-noise ratio is considerably higher for MEG measurements than for EEG measurements. Another advantage of MEG comes from the spatial attenuation of magnetic fields, which results in the

situation that a subset of magnetic sensors can be used to scan a limited brain region for dipolar patterns. In contrast, with EEG the spread of volume currents affects even distant electrodes and thus, a focal activation cannot be modeled well if other activity is present, even if this activity is spatially dispersed.

2. Method

2.1. Subjects

Data from 116 individuals served to test the method of ASWAM. Subjects had been recruited as control subjects in different studies, in which MEG was recorded as described below. Thus, data acquisition was identical for all subjects. Across studies subjects were included as 'control' only, if they had never been treated for a neurological or psychiatric disorder and were not under medication (other than vitamins or aspirin or contraceptives). All subjects were right-handed as verified by the Edinburgh Handedness Questionnaire (Oldfield, 1971). The sample consisted of 59 males (mean age 31.7 ± 10.9 , range 19–66 years) and 57 females (mean age 26.1 ± 8.5 , range 17–64 years). Subjects were informed in detail about the measurement procedure, and a written consent was obtained from every subject prior to the measurement.

2.2. Data acquisition

Using a 148-channel whole-head neuromagnetometer (MAGNESTM 2500 WH, 4D Neuroimaging, San Diego, USA) the MEG was measured during a 5 min resting period. Recordings were obtained in a supine position. Subjects were asked to relax but stay awake and not engage in any specific mental activity. They were further asked to fixate a mark on the ceiling of the magnetically shielded room throughout the recording in order to avoid eye- and head-movement. A video camera installed inside the chamber allowed monitoring the subject's behavior and compliance at any time throughout the measurement. The subject's index points and head shape were digitized with a Polhemus 3Space[®] Fasttrack prior to each measurement (the nasion point, an anatomical landmark, and the left and right ear canal points served as index points and were used to define a right-handed coordinate system, called headframe coordinate system; the *x*-axis points to the front, the *y*-axis to the left and the *z*-axis to the top of the head). The subject's headsize was measured using three parameters: ANTERIOR, which is the *x*-coordinate of nasion point; LEFTRIGHT, which is the difference of *y*-coordinate of the left and right ear canal points; SUPERIOR, which is the maximum *z*-coordinate of all digitized head shape points. The subject's head position relative to the pickup coils of the sensor was estimated before and after each measurement.

2.3. Data analysis—abnormal slow wave activity mapping (ASWAM)

Slow wave generators were identified in a semi-automated procedure with the main steps application of noise reduction, decimation, digital band pass filters, and magnetic source imag-

ing. Following noise reduction, data were screened for artifacts (e.g. eye blinks, muscle activity) by visual inspection and time periods without artifacts are selected. Data were then decimated by a factor of 16 (anti-alias filters are applied automatically in the same processing step) and digitally filtered separately for the delta (1.5–4.0 Hz) and theta (4.0–8.0 Hz; since results turned out to be identical for delta and theta frequencies, further steps of analysis and results refer to delta dipoles only) frequency band using a zero phase shift digital band pass filter (Butterworth filter of order 4).

Single equivalent current dipoles (ECD) were fitted for each time point in the selected artifact-free segments. Criteria applied for the selection of specific dipole solutions were goodness of fit (GoF, to ensure the statistical significance of the source model) and dipole moment (Q , to ensure focal nature of the underlying source based on neurophysiological consideration). Dipoles were selected by $\text{GoF} > 0.90$ (de Munck et al., 2001) and Q (10–100 nA m), which is equivalent to 0.1–1 cm² of activated cortex, and fulfills the assumption of a point source as assumed in the source model of an equivalent current dipole in a homogeneous sphere.

The dipole density was estimated within a volume with the anterior commissural (AC)–posterior commissural (PC) based coordinates— X : posterior–anterior, Y : right–left, and Z : inferior–superior. The field of view was— X : –12.0 to 10.0 (P–A), Y : –11.0 to 11.0 (R–L), Z : –11.0 to 11.0 (I–S). The volume was divided into voxels with a size of 2 cm × 2 cm × 2 cm. Hence, each volume comprises 1331 voxel. Within each voxel the selected ECD solutions were counted.

As artifact-free time periods varied between subjects, the dipole density was normalized by the subject's individual number of artifact-free (Nartfree) time points (*normalized dipole density*). Next, the distribution of dipole densities was analysed following two different strategies:

- (a) The normalized dipole density d was calculated for each subject j within each voxel i of the source volume (labeled *voxel based dipole density*, VBDD); then the logarithm of the normalized dipole density served to obtain a normal distribution across subjects (labeled LVBDD). The logarithm was computed for each voxel and each region except for those without fitted ECD (empty voxel), for which LVBDD it was set to 0. (Accordingly, such “empty” voxel did not contribute to averages in the following steps of analysis.) For further analysis and visualization LVBDD was Z-transformed for the single subjects using mean and standard deviation of LVBDD of the entire group of control subjects (labeled ZLVBDD).

The dipole density for the i th voxel and the j th subject is

$$d_{i,j} = \begin{cases} \frac{\text{Ndipoles}_{i,j}}{\text{Nartfree}_j}, & \forall \text{Ndipoles} > 0 \text{ Nartfree} > 0 \\ 0 & \end{cases},$$

$$z_{i,j} = \begin{cases} \frac{\ln d_{i,j} - \mu_i}{\sigma_i}, & \forall d_{i,j} > 0 \\ 0 & \end{cases},$$

$$\mu_i = \frac{1}{\text{Nsubjects}} \sum_j \ln d_{i,j},$$

$$\sigma_i = \frac{1}{\text{Nsubjects} - 1} \sqrt{\sum_j (\ln d_{i,j} - \mu_i)^2}$$

Results were stored in the ANALYZE™ 7.5 file format (<http://www.mayo.edu/bir/PDF/ANALYZE75.pdf>) and allowed the use of open source analysis and imaging tools.

- (b) The second strategy determines the dipole density within anatomically defined brain areas (Fig. 1; Table A.1). For this *region based dipole density* (RBDD) schemata were generated for temporal, frontal, central and parietal parts of the brain within each hemisphere following the classification of the anatomical atlas provided with MRICRO's AAL (<http://www.sph.sc.edu/comd/rorden/mricro.html>) (see Appendix 1 for the list of anatomical structures included in each of the eight regions). Within these eight regions dipole density was estimated as the average of VBDD. As for VBDD, statistical analysis of RBDD was based on the logarithm of Z-transformed, region based mean and standard deviation from the entire sample (labeled ZLRBDD). A value of 0.5/Nartfree was assigned to regions without fitted dipoles (i.e., ‘empty’ regions) before calculating the logarithm. (In contrary to (a) where it was absolutely necessary that empty voxels were assigned a value of zero, it was more convenient from a programmer's point of view to assign a value of 0.5/Nartfree. This value is unique because the smallest possible value for a “non-empty” region is 1/Nartfree. Therefore the statistics were not biased and the program does not have to keep track of empty regions.)

2.4. Statistical analysis—mixed effects model for regional Z

For the dependant variable ZLRBDD (for the sake of brevity termed Z from hereon), variance components were estimated using PROC MIXED (SAS® 9.1). Model 1 tested the fixed effects HEMI (comparing left- and right-hemispheric regions), REGION (comparing frontal, central, temporal, and parieto-occipital regions), GENDER (comparing male and female subjects) and the interaction of these factors (HEMI × GENDER, HEMI × REGION, REGION × GENDER and HEMI × REGION × GENDER). The factor subject (ID), nested in GENDER, was specified as RANDOM as well as all interactions ID × HEMI and ID × REGION. Given its small covariance estimate the random effect ID × HEMI × REGION was discarded from all models. The covariance structure “VC = variance components” was chosen.

As visual inspection of raw data suggested a linear relationship between AGE and Z (Fig. 2), the variable AGE was included as covariate (continuous predictor) in model 1. Since gender groups differed in age (females being younger than males: $t = 3.1$, $p < 0.003$) and headsize (females having smaller heads than males: LEFTRIGHT, $t = 7.1$, $p < 0.00001$; ANTERIOR,

Fig. 1. Anatomically defined brain regions based on the AAL map (Tzourio-Mazoyer et al., 2002) included in *mrinfo* (<http://www.sph.sc.edu/comd/rorden/mrinfo.html>): green = frontal, blue = temporal, yellow = parieto-occipital, red = central. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

$t=3.9$, $p<0.0002$; SUPERIOR, $t=3.3$, $p<0.002$), separate analyses were conducted using age only (models 1a and 1b) and both, age and headsize parameters (model 2) as covariates of no interest. AGE and GENDER were hierarchically separated and interactions of these two variables were not included. In order to account for the fact that covariates AGE, ANTERIOR, LEFTRIGHT, and SUPERIOR differed between groups, analy-

ses were performed separately for females and males (Miller and Chapman, 2001). Linear regression models were calculated using PROC REG (SAS[®] 9.1) for significant interactions between continuous predictors and fixed effects. It should be noted that due to the large number of variables these correlations should not be over-interpreted, since correlations tend to become more easily significant with large N .

Fig. 2. Scatterplot of Z-scores (DELTA) vs. AGE for males (left column) and females (right column).

3. Results

An average of $63,965 \pm 3178$ sample points per subject entered the analysis. The amount of artifact-free sample points was $49,339 \pm 10,314$ from which an average of 8937 ± 2352 had dipole fit solutions that met the selection criteria.

Within the entire sample, ASWA (despite slow wave activity in normal controls cannot be considered as *abnormal* the term ASWA is used as well) was small and evenly distributed. Z did not vary between regions and only slightly between hemispheres (model 1: $F=3.7$, $p<0.06$). Mean Z values of regions were always smaller than 0.4 (Fig. 3).

Still, the distribution of ASWA differed between males and females (see Fig. 4, GENDER: $F(1, 113)=4.3$, $p<0.05$): male subjects displayed higher fronto-central ASWA than females (REGION $\times$ GENDER: $F(3, 340)=12.3$, $p<0.0001$). Post hoc tests confirmed the significant difference between males and females in frontal ($t=-3.95$, Tukey–Kramer adjusted $p<0.0001$) and central ($t=-3.78$, Tukey–Kramer adjusted $p<0.0002$) regions. In addition, the deviance from the mean distribution (Z) decreased with increasing age (AGE: $F(1, 338)=8.5$, $p<0.004$). The linear correlation (PROG REG) confirmed an adjusted $r^2=0.016$ ($F(1, 455)=8.50$, $p<0.004$) for

female and an adjusted $r^2=0.048$ ($F(1, 471)=24.9$, $p<0.0001$) for male participants.

Considering gender in separate analyses (PROC MIXED models 1a and 1b) confirmed this topographical pattern of ASWA. In females the main effect REGION ($F(3, 156)=3.17$, $p<0.03$) confirmed the parieto-occipital > frontal ASWA, without significant effect of AGE. In males the main effect REGION ($F(3, 165)=6.86$, $p<0.0002$) resulted from the fronto-central dominance of ASWA, while a main effect AGE ($F(1, 157)=4.37$, $p<0.04$) verified lower ASWA in older participants. It seems noteworthy that least square estimates for ASWA differed only slightly between the models but much more importantly to a larger extend within the models (e.g. between regions).

Similarly, the gender-specific ASWA topography was substantiated after controlling for headsize by including parameters as continuous predictors (see above). Main effect and interactions with REGION remained significant for the female sample (REGION: $F(3, 156)=3.17$, $p<0.03$; AGE $\times$ HEMI $\times$ REGION: $F(3, 156)=2.69$, $p<0.05$; ANTERIOR $\times$ REGION: $F(3, 156)=17.55$, $p<0.0001$; SUPERIOR $\times$ REGION: $F(3, 156)=3.24$, $p<0.03$; ANTERIOR: $F(1, 156)=3.80$, $p<0.06$; SUPERIOR: $F(1, 156)=15.39$, $p<0.0002$), as well as for the male sample (REGION:

Fig. 3. Z-Scores for female (FL and FR) and male (ML and MR) subjects. FL and ML show the left FR and MR the right hemispheres (FL = female left, FR = female right, ML = male left, MR = male right). The outer surface of the hemispheres are displayed in the first and third column while the inner part is displayed in columns 2 and 4. Columns 1 and 2 show all Z-scores while columns 3 and 4 show only those regions where t -tests comparisons were significant ($p<0.05$; uncorrected for multiple comparisons). Colorscale ranges from -0.4 (dark blue) to 0.4 (red) while small (neutral) Z-scores have green colors. The segmented brain was calculated using the software package Caret (Van Essen et al., 2001), overlays of ASWA and the voxel based t -test results were done with AFNI/SUMA (Cox, 1996). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 4. Z-Scores in the DELTA band: (a) interaction REGION $\times$ GENDER and (b) interaction HEMI $\times$ REGION $\times$ GENDER. Males show larger Z-scores in fronto-central regions than females. Error bars indicate standard errors.

$F(3, 165)=6.86, p<0.0002$; ANTERIOR $\times$ REGION: $F(3, 157)=21.06, p<0.0002$; SUPERIOR $\times$ REGION: $F(3, 157)=7.03, p<0.0003$; SUPERIOR $\times$ HEMI $\times$ REGION: $F(3, 157)=3.62, p<0.02$; AGE: $F(1, 157)=4.37, p<0.04$; SUPERIOR: $F(1, 157)=5.56, p<0.02$). Linear single and multiple correlations between headsize parameters and dependent variables (see Tables A.2 and A.3 for specifications of the models, degrees of freedom, and results of the PROG REG models) were small (adjusted $r^2<0.1$)—strengthening the assumption, that headsize did not significantly account for the gender differences in ASWA distribution.

4. Discussion

The aim of the present article is to introduce a method for mapping generators of electromagnetic slow wave activity on a voxel-scale and for anatomically defined cortical regions. The proposed method was applied to a sample of 116 healthy subjects in order to test the method and to disclose 'normal' variations of

generator distribution with latent subject variables like gender or age. Results demonstrate the power of the method to disclose dipolar generators of slow wave activity, their distribution across cortical regions, and subtle differences in the slow wave distribution between subgroups of individuals. Further validation of the method must be complemented by its power to disclose *abnormal* slow wave clustering, that is, dipole densities exceeding those described for healthy subjects.

Though with low intensity, focal slow wave activity was present in the waking MEG in healthy individuals. Although slow wave activity in the waking state was addressed as indication of pathology in the introduction, its presence does not seem *per se* associated with abnormality. In healthy subjects, besides sleep, slow wave activity – though mainly in the 4–7 Hz theta band – can also be induced by a variety of mental activities including memory processes (Doppelmayr et al., 1998; Klimesch et al., 1996), arithmetic (Harmony et al., 1996), or processing demands (Asada et al., 1999). If aging correlates with an increase of small white-matter lesions and/or reduced neurotransmitter levels, one might expect an increase of slow wave activity with age. This slow wave activity can be expected to be of widespread nature, which means that it is only explained to a small extend by a focal source. In accordance the correlation between AGE and slow wave activity was found to be small and the direction of the relationship was opposite to the one expected. It can therefore be concluded that age does not increase ASWA measures in healthy controls. Thus, we suggest that a distribution as found in the present sample of 116 subjects may represent a 'normal' range of neuronal network communication related to a 'normal' range of personality or psychological functioning, and that specific deviances from this normal distribution might be considered markers of abnormal neuronal network activity in psychiatric disorders.

Although the combination of data from control subjects (screened for absence of neurological and psychiatric disorders) served to describe the 'normal' slow wave distribution in healthy individuals, it may be questioned, whether the present sample of 116 participants represented the 'norm'. While the data acquisition procedure was identical for all participants and gender was equally distributed in this sample, subject recruitment did not meet standards of a representative sample, and age was not equally distributed among gender groups. Still, the results disclose substantial homogeneity, which encourages to consider the present sample as representing a 'normal' distribution of slow wave activity. However, this should and will be verified by continuing subject recruitment specifically designed to establish a representative sample of healthy subjects.

Although healthy male and female participants generated slow waves with similar intensity, the topography of slow wave generators differed with male subjects exhibiting more focal slow waves in fronto-central regions than females. As subsamples differed in age and as head circumference is often smaller in females than in males, the potential confounding effect of these variables was carefully analysed. Although an impact of both variables was indeed documented, it turned out to be small, and the gender-specific ASWA pattern was confirmed after controlling for age and headsize. In particular, it cannot be ruled

out that a larger distance between the MEG sensors and the frontal cortex, as a consequence of smaller headsize in some female participants, reduce the sensitivity to detect anterior slow wave generators—hence, contributing to gender differences particularly in anterior ASWA. However, the small regression coefficients and limited explained variance suggest that gender-specific ASWA cannot be interpreted as trivial consequence of different headsizes.

Gender differences in brain structure and function have been discussed at length (Cahill, 2006), but differences not related to gender-specific processing modes (like task or test performance) and not related to psychopathology are less frequently reported. With respect to spontaneous electromagnetic activity, higher percentage of left-frontal sleep spindles (Huupponen et al., 2002) or less pronounced long-range temporal correlations between occipito-parietal and frontal EEG-alpha generators were reported for females relative to males (Nikulin and Brismar, 2005) (in both reports, gender effects were independent of age).

Thus, if we consider gender differences in ASWA topography as an indication of genuine gender differences in neuronal network communication, analyses of abnormal slow wave activity should also consider this effect not only in psychiatric patients but also in normal controls, i.e., be performed separately for male and female groups. Another possibility to take the gender-specific ASWA topography into account is to estimate correction terms, e.g. subtraction of the least square estimates of Z depending on gender, hemisphere and region as displayed in Fig. 4a and b. Gender-specific ASWA Z -scores of single subjects (e.g. patients) could then be considered to be abnormal if they are larger than 2, meaning Z is outside the range of 2 standard deviations of the Z -scores of the normal controls.

Finally, a straightforward control of the gender effect would define two control groups separate for gender. This would simplify the statistical models much as not only the factor GENDER disappears but also the continuous predictors for AGE, ANTERIOR, LEFTRIGHT, and SUPERIOR. Clinical testing of abnormal slow waves in single subjects is possible and results could be visualized using individual segmented brains. Z -scores for the normal controls, which are necessary to estimate Z -scores of individual subjects and source code to perform the analysis are available on request from the author.

In sum, testing a new method for the mapping of slow wave generators in a sample of >100 healthy subjects recommends the application of this method for the analysis of *abnormal* slow wave activity (ASWA) in subjects diagnosed with psychiatric disorders. The present results recommend a large group of normal control subjects from the age range 17–66 as basis to compare abnormal slow waves of patient samples with the aim to improve our understanding of abnormalities in neuronal network communication related to disorders, but also to assist diagnostic and prognostic purposes.

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Appendix A

See Tables A.1–A.3.

Table A.1

Anatomical structures assigned to the four regions used for the calculation of RBDD

Left		Right	
No.	AAL region	No.	AAL region
Central			
1	Precentral_L	2	Precentral_R
19	Supp_Motor_Area_L	20	Supp_Motor_Area_R
33	Cingulum_Mid_L	34	Cingulum_Mid_R
57	Postcentral_L	58	Postcentral_R
59	Parietal_Sup_L	60	Parietal_Sup_R
61	Parietal_Inf_L	62	Parietal_Inf_R
63	SupraMarginal_L	64	SupraMarginal_R
65	Angular_L	66	Angular_R
69	Paracentral_Lobule_L	70	Paracentral_Lobule_R
Parieto-occipital			
35	Cingulum_Post_L	36	Cingulum_Post_R
43	Calcarine_L	44	Calcarine_R
45	Cuneus_L	46	Cuneus_R
47	Lingual_L	48	Lingual_R
49	Occipital_Sup_L	50	Occipital_Sup_R
51	Occipital_Mid_L	52	Occipital_Mid_R
53	Occipital_Inf_L	54	Occipital_Inf_R
67	Precuneus_L	68	Precuneus_R
Frontal			
3	Frontal_Sup_L	4	Frontal_Sup_R
5	Frontal_Sup_Orb_L	6	Frontal_Sup_Orb_R
7	Frontal_Mid_L	8	Frontal_Mid_R
9	Frontal_Mid_Orb_L	10	Frontal_Mid_Orb_R
11	Frontal_Inf_Oper_L	12	Frontal_Inf_Oper_R
13	Frontal_Inf_Tri_L	14	Frontal_Inf_Tri_R
15	Frontal_Inf_Orb_L	16	Frontal_Inf_Orb_R
21	Olfactory_L	22	Olfactory_R
23	Frontal_Sup_Medial_L	24	Frontal_Sup_Medial_R
25	Frontal_Mid_Orb_L	26	Frontal_Mid_Orb_R
27	Rectus_L	28	Rectus_R
31	Cingulum_Ant_L	32	Cingulum_Ant_R
71	Caudate_L	72	Caudate_R
Temporal			
17	Rolandic_Oper_L	18	Rolandic_Oper_R
29	Insula_L	30	Insula_R
37	Hippocampus_L	38	Hippocampus_R
39	ParaHippocampal_L	40	ParaHippocampal_R
41	Amygdala_L	42	Amygdala_R
55	Fusiform_L	56	Fusiform_R
73	Putamen_L	74	Putamen_R
79	Heschl_L	80	Heschl_R
81	Temporal_Sup_L	82	Temporal_Sup_R
83	Temporal_Pole_Sup_L	84	Temporal_Pole_Sup_R
85	Temporal_Mid_L	86	Temporal_Mid_R
87	Temporal_Pole_Mid_L	88	Temporal_Pole_Mid_R
89	Temporal_Inf_L	90	Temporal_Inf_R

Definition of regions was based on the AAL map (Tzourio-Mazoyer et al., 2002) included in MRICRO (<http://www.sph.sc.edu/comd/rorden/mricro.html>).

Table A.2

 r^2 and adjusted r^2 for single and multiple correlation models

Gender	Model	r^2	Adjusted r^2	DF model	DF error	F	p
Female	Z= AGE	0.0184	0.0162	1	454	8.50	0.0037
Female	Z= ANTERIOR	0.0139	0.0118	1	454	6.41	0.0117
Female	Z= LEFTRIGHT	0.0049	0.0027	1	454	2.24	n.s.
Female	Z= SUPERIOR	0.0795	0.0774	1	454	39.19	<0.0001
Male	Z= AGE	0.0503	0.0483	1	470	24.90	<0.0001
Male	Z= ANTERIOR	0.0001	−0.0020	1	470	0.04	n.s.
Male	Z= LEFTRIGHT	0.0103	0.0082	1	470	4.90	0.0273
Male	Z= SUPERIOR	0.0458	0.0438	1	470	22.57	<0.0001
Female	Z= AGE, ANTERIOR, LEFTRIGHT, SUPERIOR	0.1126	0.1048	4	451	14.31	<0.0001
Male	Z= AGE, ANTERIOR, LEFTRIGHT, SUPERIOR	0.1023	0.0947	4	467	13.31	<0.0001

Table A.3

 r^2 and adjusted r^2 for different multiple correlation models, within hemispheres and regions (model: Z= AGE ANTERIOR LEFTRIGHT SUPERIOR)

Gender	HEMI	REGION	r^2	Adjusted r^2	DF model	DF error	F -value	p
Female	Left	Central	0.2513	0.1937	4	52	4.36	0.0041
Female	Left	Frontal	0.2395	0.1810	4	52	4.09	0.0058
Female	Left	Parocc	0.4151	0.3701	4	52	9.23	<0.0001
Female	Left	Temporal	0.0994	0.0301	4	52	1.43	n.s.
Female	Right	Central	0.3188	0.2664	4	52	6.08	0.0004
Female	Right	Frontal	0.3571	0.3076	4	52	7.22	0.0001
Female	Right	Parocc	0.3994	0.3532	4	52	8.65	<0.0001
Female	Right	Temporal	0.2231	0.1633	4	52	3.73	0.0096
Male	Left	Central	0.3396	0.2907	4	54	6.94	0.0001
Male	Left	Frontal	0.3171	0.2665	4	54	6.27	0.0003
Male	Left	Parocc	0.1898	0.1298	4	54	3.16	0.0209
Male	Left	Temporal	0.0241	−0.0482	4	54	0.33	n.s.
Male	Right	Central	0.3675	0.3206	4	54	7.84	<0.0001
Male	Right	Frontal	0.4481	0.4072	4	54	10.96	<0.0001
Male	Right	Parocc	0.2410	0.1847	4	54	4.29	0.0044
Male	Right	Temporal	0.0753	0.0068	4	54	1.10	n.s.

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