Fehr,T., Achtziger,A. Hinrichs,H. & Herrmann, M. (2003, in press) Interindividual differences in oscillatory brain activity in higher cognitive functions - Methodological approaches in analyzing continuous MEG data. In: Reinvang,I., Greenlee,M.W. & Herrmann, M. (Eds.) *The Cognitive Neuroscience of Individual Differences*. Oldenburg: bis-Publishers

Interindividual differences in oscillatory brain activity in higher cognitive functions - Methodological approaches in analyzing continuous MEG data

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Summary: Interindividual differences of psychophysiological parameters often exceed the possibilities of the methods used in analyses. Both the subtle nature of higher cognitive functions due to the complexity of the underlying neural networks as well as the relatively small measurable physiological signals require appropriate and sensitive strategies in analyzing the data. Therefore a better definition of the topic that actually has to be examined in the data set might be helpful. In order to get a better approach to that issue we introduced a model-based multiple dipole-density strategy on bandpass filtered continuous MEG data recorded during three different mental tasks. The frequency ranges were individually determined by preselection of the power spectra of the data sets. In comparison to three alternative methods performed on bandpass filtered data of fixed frequency bands the proposed strategy leads to a better regional characterization of the different mental conditions.

Introduction: It is a well known fact that methodological problems in psychophysiological data very often arise by Interindividual differences due to the variations in statistical procedures. Even in well defined paradigms that analyze specific electrophysiological aspects (e.g. tonotopic brain maps) interindividual differences often play a crucial role. The problem becomes more severe when continuous data have to be analyzed. Additionally, complexity in the data set reflecting the complexity of higher cognitive functions makes it difficult to model the underlying hypotheses. Dipole-density and minimum-norm algorithms were successfully used on continuous bandpass filtered data to examine differences between psychiatric patients [1] and controls and/or to determine pathologic foci e.g. of brain lesions [2,3]. Activation patterns in relation to pathology are mostly characterized by high amplitudes and, therefore, be examined by relatively insensitive methods. The same strategies, however, are not adequate to assess more subtle and presumably more interindividual differences in higher cognitive functions with high accuracy. The preselection of specific individual properties of the data might be helpful to find the topic that actually has to be examined. This work shortly describes four strategies in analyzing continuous MEG data acquired during three mental conditions.

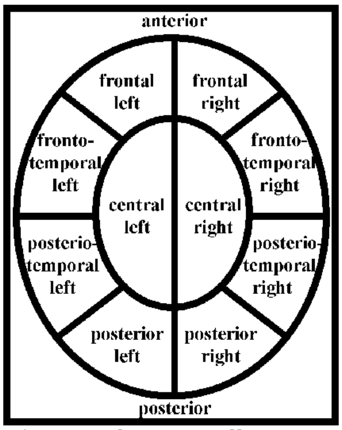

Fig.1: *Schematic illustration of the ten regions used to cluster the power data.*

Methods:

Data acquisition, subjects and tasks: Whole-head (148 channels) magnetoencephalographic recordings (MAGNES® 2500 WH, 4D Neuroimaging, San Diego, USA) were obtained from 9 healthy female adults (mean age: 22.6±5.2 yrs.; 20-27 yrs.) during a resting condition and two conditions during which the subjects had to perform mental activities. These activities consisted of luxuriation/indulging in positive fantasies and contrasting positive fantasies with real-life decisions during their study at the university (in detail described elsewhere; Achtziger, in prep.).

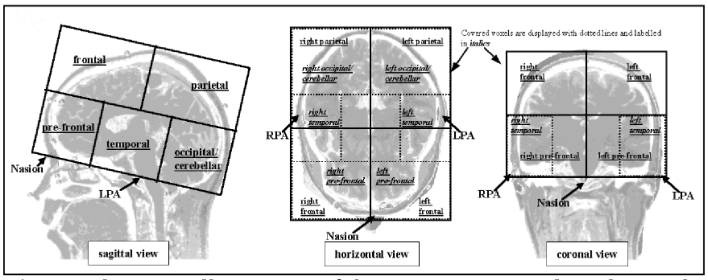

Fig.2: *Schematic illustration of the ten regions used to cluster the dipole density (DDP) data.*

Subjects were asked to fixate a colored fixation point on the ceiling of the chamber in order to reduce eye- and head-movements. The MEG was recorded with a 678.17 Hz sampling rate, using a band-pass filter of 0.1-200 Hz. The total recording time for each condition was 5 minutes. For artefact control, eye movements (EOG) were recorded from four electrodes attached to the left and right outer canthus and above and below the right eye.

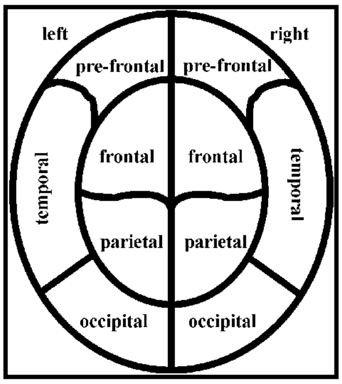

Fig.3: *Schematic illustration of the ten regions used to cluster the mini-mum-norm (MMN) data.*

Regional Fast Fourier Transformation (FFT): For each subject a Fast Fourier Transformation (FFT) was performed. FFT results were averaged over all 148 MEG-channels and then divided in 17 frequency bands: delta [1.5-4Hz], theta [4-8Hz], alpha-low [8-10.5Hz], alpha-high [10.5-13Hz], beta-low [13-21.5Hz], beta-high [21.5-30Hz] and 11 gamma bands (width 6 Hz) between 30 and 100 Hz

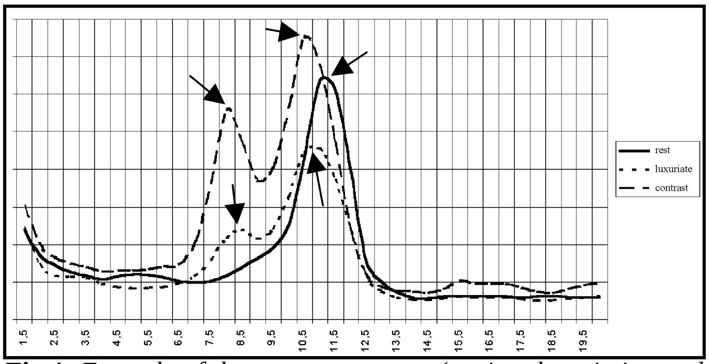

Fig.4: *Example of three power spectra (resting, luxuriating and contrasting) of one subject. The different conditions show several specific deflections.*

(without 48-50 Hz). To get regional power values of each data set separately FFT results were averaged for 10 channel groups (see fig. 1). Absolute and relative global and regional FFT band power was analyzed by ANOVAs examining regional and frequency band related condition differences.

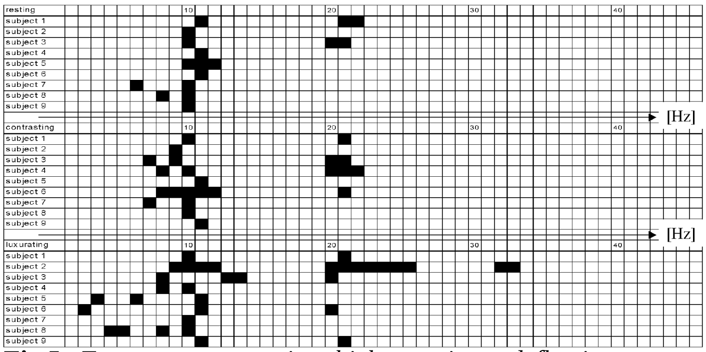

Fig.5: *Frequency ranges in which prominent deflections occur were shadowed for each subject and condition.*

Dipole Density (DD): Time segments - low on artefacts - of band-pass (delta [1.5-4.0 Hz] and theta [4.0-8.0Hz]) filtered data were determined by visual inspection. Single equivalent dipoles in a homogeneous sphere were fitted for each time point only in the selected epochs of various length. All 148

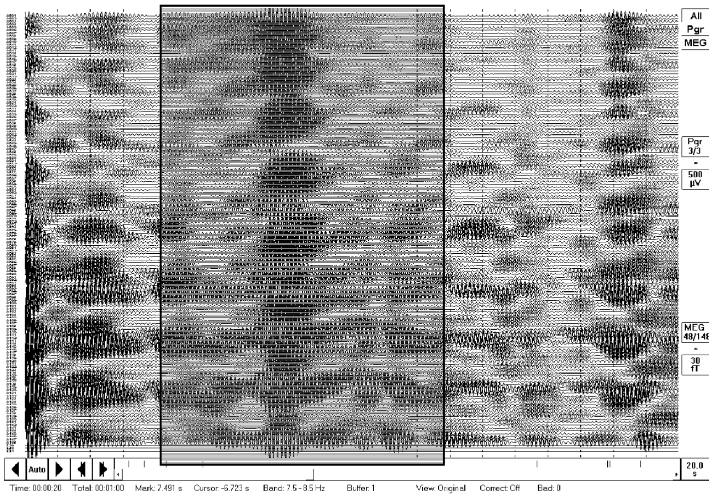

Fig.6: *Example for selected time epoche (box) of bandpass-filtered data in which all channels (wave forms arranged in lines) show clear activity.*

channels were used for source estimation. Only dipole fit solutions at time points with a root mean square between 100 and 300 ft, a goodness of fit (GOF) over 0.90 and a dipole moment over 50nAm were accepted for further analysis. For statistical analysis the brain was divided into ten regions of interest (ROI, see fig. 2). The percentage of time during which a dipole model would fit in the delta and in the theta band was determined for each subject, condition and region.

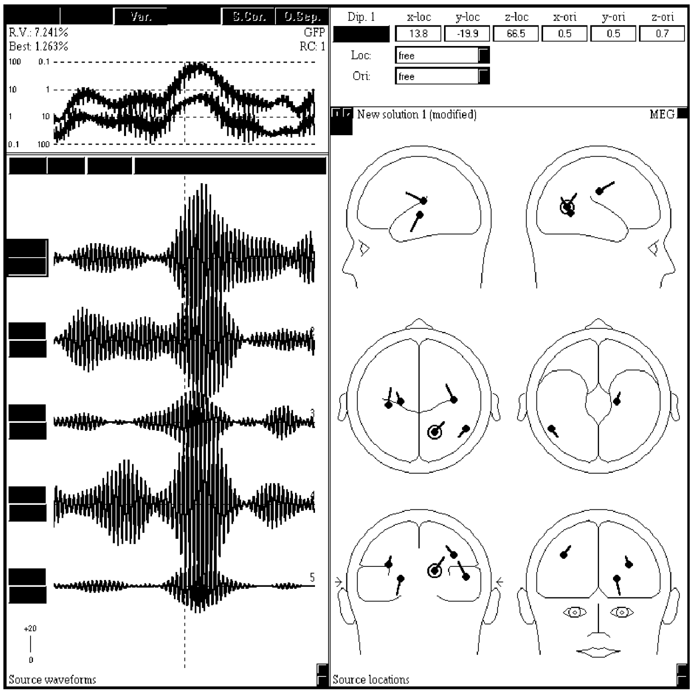

Fig.7: *Source wave forms and locations of a 5-dipole modell based on a 6 second bandpass filtered data epoche.*

Minimum Norm L2 (MMN): For multiple source detection the MMN-method [4,5] was performed on a 30 second band-pass filtered (delta [1.5-4.0 Hz], theta [4.0-8.0 Hz], alpha low [8.0-10.5 Hz], alpha high [10.5-13.0 Hz], beta [18-22 Hz], gamma1 [28-32 Hz] and gamma2 [38-42 Hz]) data epoch for each subject and condition. Over all data time points with a global field power between 3000 and 18000 fT that did not correlate with a prominent eye-blink pattern a MMN solution was calculated. MMN values were estimated at 87 positions (each consisting of two orthogonal dipoles tangentially oriented to the surface) on a concentric shell that was computed as a rough approximation of the brain volume. Thereafter, the source activity of each position was collapsed by averaging the absolute values of both dipole orientations.

The MMN solutions were then averaged over all data time points. For statistical analyses the resulting MMN-Maps were attributed to 10 ROIs by averaging clusters of MMN-values roughly representing particular brain regions (see fig. 3). The whole procedure was also performed on the lower, middle and stronger magnetic fields of each data set separately. First for each band-pass filtered data set the global field power of each data time point was calculated and the highest global field power value was determined. Thereafter, minimum-norm estimates were calculated separately for the lower, middle and higher third activity data time points and averaged for statistical proceedings.

Multiple Dipole Density (MDD):

1.) For each subject and condition a fast fourier transformation (FFT) was performed on the data. FFT results were averaged over all 148 MEG-channels. The resulting power spectra were plotted for each subject and condition (see fig. 4).

2.) Power spectra were visually inspected and prominent deflections of each spectrum were noted as possible effects of generators underlying background and/or condition related activity (see fig. 4 [arrows] and fig. 5 for critical frequency ranges).

3.) Original data sets were bandpass filtered separately for all critical frequency bands and visually inspected for epochs in which all channels show activity (e.g. fig. 6). More precise, data were filtered 1 Hz around identifiable peaks in the power spectrum or for more extensive cohesive frequency ranges in which a particular condition clearly showed more power than the others. In those epochs (about 5 seconds) stepwise multi-dipole analysis was performed using the software BESA2000. First a spatio-temporal PCA was calculated to get a first impression of how many dipoles approximately have to be expected to explain the data in the actual model. During the next step the epoch with the highest deflections in the eigen-value curve was marked to fit the first dipole(s). Thereafter, additional dipoles were added one by one and fitted on partial epochs showing the highest residuals. The number of dipoles was increased until 90 percent of variance was explained (by a maximum of 15 dipoles, see fig. 7 for illustration).

Afterwards, all dipoles were fitted simultaneously for the whole epoch to tune the position of each dipole in the model.

In dipole fit procedures using the BESA software dipoles were first set to different positions in order to search the best starting position. This prevents that dipoles are fitted to local minima.

all data time points averaged (condition x region; F(18,216)=F)				
band [Hz]	F	p	GG	HF
delta [1.5-4.0]	.21	.82	.99	.99
theta [4.0-8.0]	.67	.70	.91	.94
alpha low [8.0-10.5]	.50	.62	.77	.80
alpha high [10.5-13.0]	.39	.69	.85	.88
beta [18.0-22.0]	.19	.83	.94	.96
gamma 1 [28.0-32.0]	.54	.59	.80	.84
gamma 2 [38.0-42.0]	.61	.55	.76	.80

Tab 1: *ANOVAs over regional MMN-values of several frequency bands; uncorrected (p), Greenhouse-Geisser (GG) and Huynh-Feldt (HF) corrected p-values.*

Fitting the first single dipole sometimes resulted in a dipole position located in the middle of the sphere model. Those solutions often represent a sum of source activities at different positions around. This could be confirmed by the huge moment of those dipoles that could not be generated by a valid physical source in the middle of the brain. A manual arrangement of two or three dipoles in positions around the center of the sphere often provided a more appropriate starting condition for the fitting procedure.

Oscillatory activity in gamma range (above 30 Hz) could not be fitted using the model criteria and were therefore excluded of further analyses.

4.) The multi-dipole model reaching the criterion explained above was then used to fit the complete data (60 seconds) epoch. The resulting source wave forms served as a basis for the statistical analysis.

5.) For statistical analyses the brain was divided into ten ROIs (comparable to fig.2). In a first approach each data time point of the source wave forms was examined as follows: assuming, n is the number of dipoles in the present model, a dipole has to reach more than the n-th part of the sum of current equivalents at that data time point to be considered for statistics. Thereafter, the regional densities of dipoles were then calculated with

low GFP data time points averaged (condition x region; F(18,216)=F)				
band [Hz]	F	p	GG	HF
delta [1.5-4.0]	.24	.79	.95	.98
theta [4.0-8.0]	.47	.63	.86	.89
alpha low [8.0-10.5]	.45	.65	.86	.90
alpha high [10.5-13.0]	.34	.71	.90	.93
beta [18.0-22.0]	1.00	.38	.44	.44
gamma 1 [28.0-32.0]	.67	.52	.70	.73
gamma 2 [38.0-42.0]	.73	.49	.66	.70

Tab 2: *ANOVAs over regional MMN-values (only time points with low GFP) of several frequency bands; uncorrected (p), Greenhouse-Geisser (GG) and Huynh-Feldt (HF) corrected p- values*

respect to differences in mental conditions by ANOVAs.
The central aspect of the described strategy consisted in bypassing the problem of high interindividual variability of activities within fixed ranges of frequency bands. Based on the assumption that subjects proceed in different frequency bands but in the same ROIs due to the same semantic condition a FFT was performed in order to determine individual task-related frequency ranges of activity for each data set. Afterwards only those frequency ranges were analyzed in terms of source analyses. Considering interindividual differences in oscillatory brain activity consistent task-related regional variations should be.

middle GFP data time points averaged (condition x region; F(18,216)=F)				
band [Hz]	F	p	GG	HF
delta [1.5-4.0]	.24	.79	.98	.99
theta [4.0-8.0]	.57	.58	.76	.80
alpha low [8.0-10.5]	.63	.54	.73	.76
alpha high [10.5-13.0]	.39	.68	.88	.91
beta [18.0-22.0]	.63	.54	.70	.74
gamma 1 [28.0-32.0]	.65	.53	.70	.74
gamma 2 [38.0-42.0]	.81	.47	.59	.62

Tab 3: *ANOVAs over regional MMN-values (only time points with medium GFP) of several frequency bands; uncorrected (p), Greenhouse Geisser (GG) and Huynh-Feldt (HF) corrected p-values*

Results:

Regional Fast Fourier Transform (FFT): ANOVAs calculated over regional absolute (REGION x FREQUENCY-BAND x CONDITION: F[288,3456]=.41, p=.67; Greenhouse Geisser (GG): p=.87; Huynh-Feldt (HF): p=.90) and relative (REGION x FREQUENCY-BAND x CONDITION: F[288,3456]=.86, p=.59; GG: p=.89; HF: p=.94) power values clearly did not reach significance. Exploratory post hoc least significance tests only showed trends but no significant differences between the conditions.

high GFP data time points averaged (condition x region; F(18,216)=F)				
band [Hz]	F	p	GG	HF
delta [1.5-4.0]	1.11	.35	.36	.36
theta [4.0-8.0]	.65	.53	.69	.72
alpha low [8.0-10.5]	.50	.61	.80	.84
alpha high [10.5-13.0]	.27	.76	.95	.97
beta [18.0-22.0]	.51	.61	.80	.84
gamma 1 [28.0-32.0]	.68	.52	.69	.73
gamma 2 [38.0-42.0]	.55	.59	.84	.89

Tab 4: *ANOVAs over regional MMN-values (only time points with high GFP) of several frequency bands; uncorrected (p), Greenhouse Geisser (GG) and Huynh-Feldt (HF) corrected p- values*

Dipole Density Plot (DDP): As shown by Achtziger (in prep.) luxuriating/indulging and contrasting generally reduced delta dipole density relatively to the rest condition. These changes, however, did not reach significant main effects or interactions. There was still a tendency for the contrasting condition to reduce delta activity mainly in right hemispheric frontal, pre-frontal and temporal regions when compared to the luxuriating condition.

MDD – multiple source density		
region	**left**	**right**
pre-frontal	cont>rest *	
frontal		cont>rest ** cont>lux **
temporal	cont>rest ** cont>lux **	cont>rest ** cont>lux **
parietal		cont>rest * cont>lux *
occipital	cont>rest *	cont>rest ** cont>lux *

Tab. 5: *least significant differences tests; rest=resting; cont=contrasting; lux=luxuriating; *=p<.05; **=p<.001*

Minimum Norm L2 (MMN):
ANOVAs calculated over regional minimum-norm (FREQUENCY-BAND x REGION x CONDITION: F[108,1296]=.38, p=.71; Greenhouse Geisser (GG): p=.97; Huynh-Feldt (HF): p=.99) values clearly did not reach significance (see table 1 for details). Exploratory post hoc least significance tests only showed trends but no significant differences between the conditions.

ANOVAs calculated over regional minimum-norm values estimated over weak (FREQUENCY-BAND x REGION x CONDITION: F[108,1296]=.39, p=.69; GG: p=.97; HF: p=.99), medium (FREQUENCY-BAND x REGION x CONDITION: F[108,1296]=.48, p=.63; GG: p=.91; HF: p=.95) and stronger (FREQUENCY-BAND x REGION x CONDITION: F[108,1296]=.51, p=.61; GG: p=.91; HF: p=.96) magnetic fields (global field power=GFP, see methods) separately did not reach significance (see tables 2, 3, 4 for details). Exploratory post hoc least significance difference tests only revealed trends but no significant differences between the conditions.

region	hemisphere	rest	luxuriating	contrasting
pre-frontal	**left**	28±39	53±87	354±649
	right	109±165	67±122	205±328
frontal	**left**	112±150	163±193	253±206
	right	430±307	480±482	1054±1084
temporal	**left**	226±174	415±510	1004±985
	right	383±406	491±481	1271±1068
parietal	**left**	30±60	88±98	114±121
	right	35±47	26±42	372±344
occipital	**left**	45±56	135±139	355±350
	right	76±93	180±152	530±668

Tab. 6: *MDD – group means of regional "dipoles per second"-values and standard deviations for ten ROIs.*

Multiple Dipole Density (MDP): The subjects showed specific deflections in the power spectra due to the different conditions (see fig. 4, 5). Oscillatory activity in the gamma range (above 30 Hz) could not be fitted using the maximum criterion of 15 dipoles and were therefore excluded of further analyses. At mean there were 5.4 (±2.8) dipole locations fitted per model. Subjects showed 14.9 (±8.4) dipole locations over all models. 2.0 (±0.8) frequency bands were examined per condition and subject.

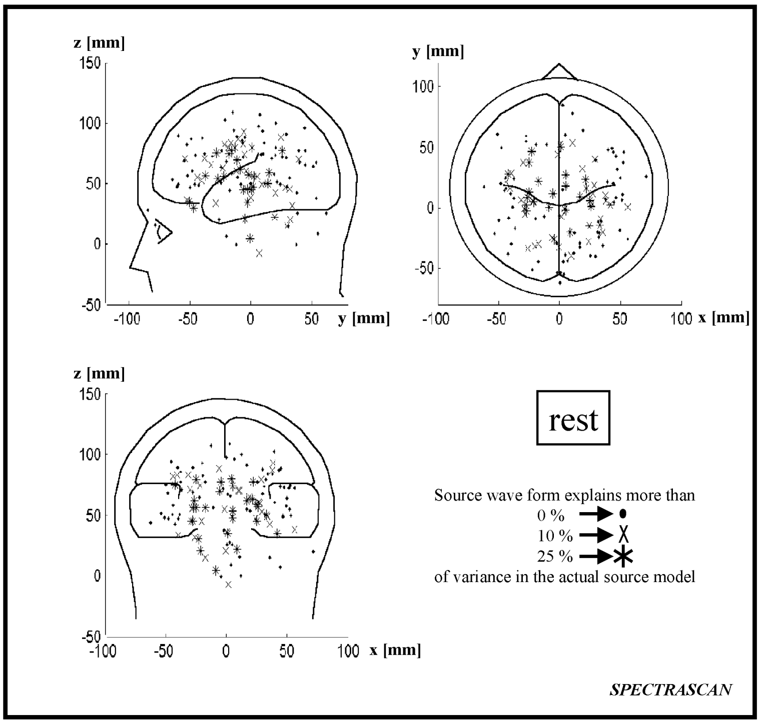

***Fig. 8:** plotted multiple dipole locations (MDD) over all subjects weighted due to the source wave forms; rest condition*

For multiple dipole density (fitted dipoles per second) in the ten ROIs (see fig. 2) a significant CONDITION x REGION (ANOVA) effect could be shown ($F(18,216)=1.98$; $p<.05$) for uncorrected statistics. Greenhouse-Geisser ($p<.10$) and Huynh-Feldt ($p<.10$) correction lowered the main effect to a trend. Post hoc analyses showed significant more dipoles per second for the contrasting condition than in the resting and the luxuriating condition especially in right frontal and temporal regions (for details see tab. 5; illustration see fig. 8-10).

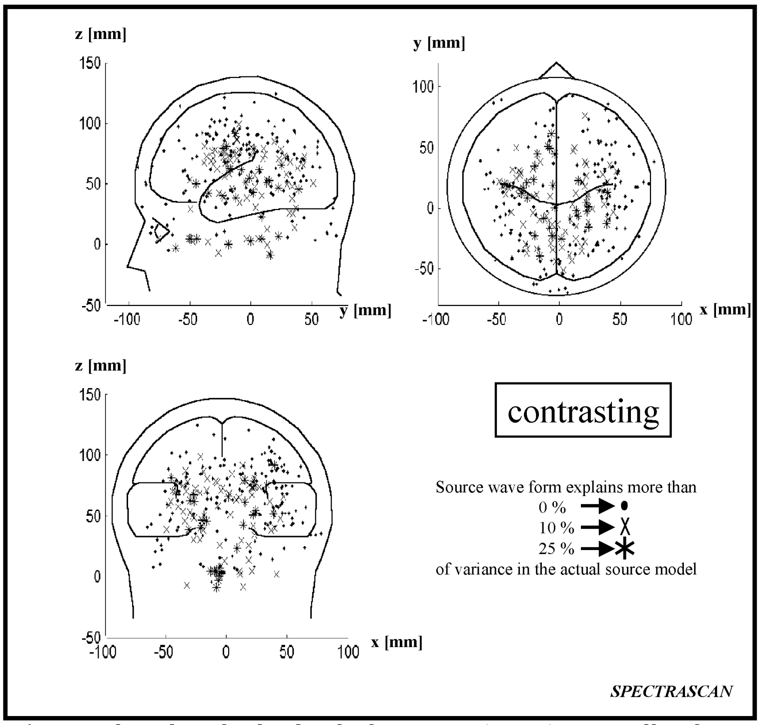

Fig. 9: *plotted multiple dipole locations (MDD) over all subjects weighted due to the source wave forms; contrasting condition*

Conclusions and Discussion

The present data clearly indicate that the finally performed strategy (MDD) based on the knowledge of individual oscillatory deflections in the power spectra and multi-dipole analyses leads to a solution that allows a good regional characterization of the different mental conditions. Further investigations have to show reliability and validity of the performed strategy of data analysis.

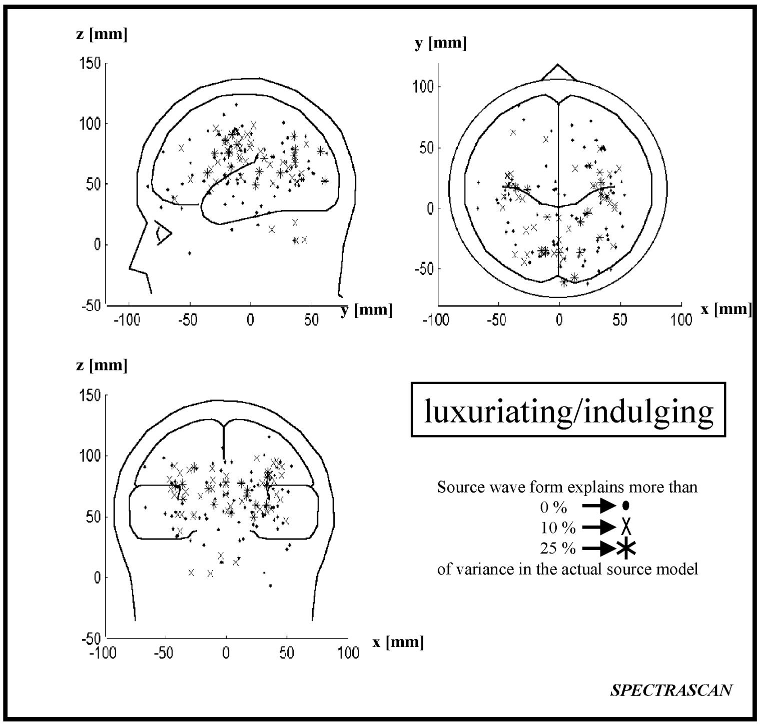

Fig. 10: *plotted multiple dipole locations (MDD) over all subjects weighted due to the source wave forms; luxuriating condition*

Several aspects of this approach have to be improved. Power spectrum ranges above 30 Hz usually need more than 15 dipoles to be fitted and, therefore, they were handled as diffuse activities and excluded from further analyses. Signals in higher frequency bands reflecting brain activity become less pronounced in comparison to the noise in higher frequency bands. This fact leads to a less pronounced identification when compared to the oscillatory brain activity of lower frequency ranges. Thus, an *exhaustive* analysis of oscillatory brain activity in a higher frequency range remains underestimated. A combination of both methods might be helpful in this case. According to the subtle nature of higher oscillatory activity methods like LORETA (Pasqual-Marqui, 1994) are possibly more appropriate in characterization of a more distributed and weak brain activity. The LORETA algorithm aims at 3-dimensional distributions of current density without making assumptions regarding the number of sources. At present, an appropriate method fitting all our requirements is not available. In the same way, an expansion of the criterion for the amount of dipoles (more than 15) might be helpful. It has to be noted that this criterion is set in an arbitrary way.

The decision of the respective relevance of a frequency band should be automized in order to enhance the objectivity of the method. In the present study simple visual inspection provided the basis for the used band-pass filters.

Multiple dipole density (MDD) was generated by only recognizing dipole locations with source wave forms reaching more than their n-th part of the current equivalent at all time points. Absolute criteria using "current equivalent" or "variance of explanation" thresholds might be also a topic of discussion. At present, however, there is a lack of information with respect to valid normative thresholds. Further investigations will have to develop appropriate criteria.

To provide a comparable parameter for the *multiple-dipole-density* statistics the amount of dipoles counted were transformed into *dipoles per second*. Different subjects, however, showed a different number of generators and dipole locations across the conditions.

To avoid statistical biases due to the use of redundant information arising from different frequency ranges relationships between activities in different frequency bands should be examined and possible relationships based on harmonics between activities of different frequency ranges should be considered in further processing.

This work definitely compared the output of different *strategies* in analyzing continuous data and not the actual used *methods*. If *dipole-density* and *minimum-norm* would be performed on the same well pre-defined band-pass filtered data sets as the *multi-dipole-density* method they could possibly provide a more appropriate data basis for better regional discrimination, too. This remains to be checked.

Although there was no explicit hypothesis making assumptions of the regional distribution of brain activity mirroring mental luxuriating or contrasting processes it can be remarked that the subjects showed more source activity in widespread right hemispheric and right temporal regions during contrasting. Brain activity during luxuriating was similar to that during the resting state. Possibly luxuriating leads to a certain state of relaxation or subjects automatically generate positive fantasies during resting or both.

In the present study different methods and strategies were used exploratively. To the present time the MDD strategy is used in a different work with a hypothetical background.

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Acknowledgments

We kindly thank Prof. Dr. Gollwitzer and Prof. Dr. Rockstroh from the University of Konstanz, Germany, for providing the data for the methodological approach used in the present article.