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A Graph-Theoretical Analysis Algorithm for Quantifying the Transition from Sensory Input to Motor Output by an Emotional Stimulus *

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Abstract— **Graph-theoretical analysis algorithms have been used for identifying subnetworks in the human brain during the Default Mode State. Here, these methods are expanded to determine the interaction of the sensory and the motor subnetworks during the performance of an approach-avoidance paradigm utilizing the correlation strength between the signal intensity time courses as measure of synchrony. From functional magnetic resonance imaging (fMRI) data of 9 healthy volunteers, two signal time courses, one from the primary visual cortex (sensory input) and one from the motor cortex (motor output) were identified and a correlation difference map was calculated. Graph networks were created from this map and visualized with spring-embedded layouts and 3D layouts in the original anatomical space. Functional clusters in these networks were identified with the MCODE clustering algorithm. Interactions between the sensory sub-network and the motor sub-network were quantified through the interaction strengths of these clusters. The percentages of interactions involving the visual cortex ranged from 85 % to 18 % and the motor cortex ranged from 40 % to 9 %. Other regions with high interactions were: frontal cortex (19 ± 18 %), insula (17 ± 22 %), cuneus (16 ± 15 %), supplementary motor area (SMA, 11 ± 18 %) and subcortical regions (11 ± 10 %).Interactions between motor cortex, SMA and visual cortex accounted for 12 %, between visual cortex and cuneus for 8 % and between motor cortex, SMA and cuneus for 6 % of all interactions. These quantitative findings are supported by the visual impressions from the 2D and 3D network layouts.**

I. INTRODUCTION

In recent years, considerable interest and activity has focused on revealing the organization and interrelationship of spatially distinct brain regions, i.e. their functional connectivity [1] by a variety of statistical methods. A subgroup of these methods attempt to quantify correlations between brain regions, for example, independent component analysis (ICA) and principal component analysis (PCA) [2], In addition, graph-theoretical network methods have been utilized, to identify functional subunits during the resting state or default mode state of the brain [3].

Here, we present the application of graph-theoretical network methods for identifying functional subclusters during the execution of an approach-avoidance paradigm. The focus of this study is to identify brain regions with high synchrony with the sensory input (sensory subnetwork) and brain regions with high synchrony with the motor output (motor network) and the quantification of the interaction strength of both.

II. MATERIALS AND METHODS

A. fMRI Paradigm

Approval of the institutional review board was obtained for this prospective study. In nine healthy volunteers, 6 male, average age: 34.7±7.5), brain regions that show fMRI activation and deactivation were identified at rest and during an approach-avoidance situation (figure 1). With the subject in the resting state for 50 seconds watching a green screen, images of faces (Eckert faces) were presented (10 repetitions, total duration 10 min) that were interpreted by the subjects as either unpleasant or pleasant. Subjects could remove a presented face that elicited an unpleasant emotional response by squeezing a ball with the right hand. The image of the face remained for a minimum of 10 seconds and it was necessary to squeeze the ball for 10 seconds to have the face disappear.

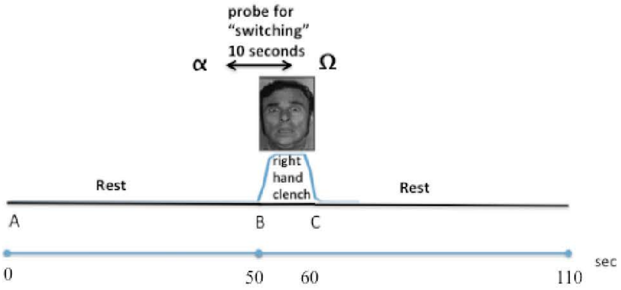

Figure 1: Paradigm for evoking an emotionally motivated motor response: A-B, rest state - 50 seconds. Green background was shown. B-C, active state – 10 seconds. Display of face. The image could be removed by the subject by squeezing a ball with his right hand, see text below.

The time course of the BOLD signals was recorded to determine the sequence of activation and deactivation of brain regions. Axial slices (echo planar imaging, echo time TE=30 ms, repetition time TR=1300 ms, field of view FOV= 210x210 mm, acquisition matrix 32x64 resulting in an interpolated in-plane resolution of 3.3 mm, slice thickness 5 mm, Siemens Verio 3T, Siemens Medical Solutions, Erlangen, Germany, fMRI equipment NordicNeuroLab, Inc.).

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B fMRI Image Post-Processing

Individual fMRI activation maps were calculated for each subject using AFNI (NIH) via the general linear model (GLM) after the following preprocessing steps: slice-time correction, motion correction, spatial blurring (full with at half maximum of the Gaussian blurring function of 3 mm), band-pass filtering (0.01 Hz to 0.1 Hz to remove very slow spatial frequencies such as drifts in the baseline and to remove high-intensity noise). The ideal response function was modeled to include an active period (10 seconds) only for faces which were perceived as unpleasant by the subject and which prompted the subject to squeeze the ball (monitored by feedback electronics in the control room by the investigator). An average fMRI activation map was calculated and transformed into Talairach space (@auto_tlrc, AFNI).

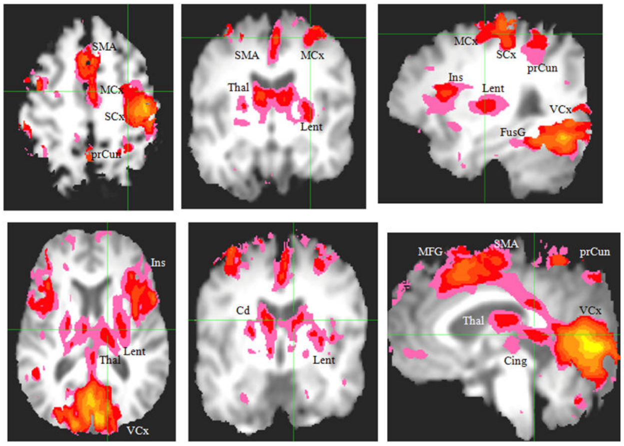

Figure 2: Task-related fMRI average activation map showing regions with a high BOLD signal. VCx: visual cortex, preCun: precuneus, Thal: thalamus, Lent: lentiform nucleus, FusG: fusiform gyrus, Ins: insula, Cd: caudate, Cing; cingulate cortex, MFG: middle frontal gyrus, SMA: supplementary motor area, SCx: sensory cortex, MCx: motor cortex.

C Graph-Theoretical Analysis

For each subject, two signal-intensity time-courses were extracted, one from the visual cortex exhibiting signal increase during the presentation of each face (visual stimulation) and one from the motor cortex where signal increase was observed only when a motor output occurred, i.e. during the presentation of an unpleasant face. A correlation difference map was calculated yielding positive difference values for regions of stronger correlation with the sensory input time course than with the motor output time course.

Employing the R statistical language, individual network adjacency matrices (A_{ij}, $i=1,..,n;\ j=1,..,n;\ n$: number of voxels) were defined as the correlation matrices for individual voxel-intensity time-courses (discarding any correlation coefficient (CC) with absolute value lower than 0.75 in the correlation difference maps): $A_{ij}=CC_{ij}> 0.75$, 0 otherwise, where CC_{ij} represents the Pearson correlation coefficient between the voxel-intensity time course of voxels i and j. The adjacency matrices were stored as graphs (gml format). The threshold of 0.75 was identified from a sensitivity analysis (data not shown). Graphs were imported into Cytoscape (version 2.8.1, www.cytoscape.org) and network clusters were identified using the Molecular Complex Detection (MCODE) algorithm [4] as implemented in the Cytoscape ClusterViz plugin emphasizing the separation of the fMRI activation into functionally distinct units. Interactions between the sensory sub-network and the motor sub-network were then quantified through the interaction strengths of these clusters by constructing separate cluster networks. The Pearson correlation coefficient of the average voxel-intensity time course of all voxels in one cluster was used as a measure of interaction strength between clusters. Interactions lower than a threshold than 0.75 were discarded. Networks were visualized using 2D spring-embedded layouts and 3D layouts in the original anatomical space.

III. RESULTS

A. fMRI Activation Maps

All subjects experienced the same five of the ten faces as unpleasant. Task-related activation was found in the visual cortex, the precuneus, the thalamus, the lentiform nucleus, the caudate, the cingulate cortex, the fusiform gyrus, the insula, the supplementary motor cortex, the sensory cortex and the motor cortex (figure 2)..

B. Synchrony of Brain Regions

Brain regions that showed a stronger synchrony (interaction) with the signal-time course of the visual cortex were additional locations in the visual cortex, the bilateral cuneus, precuneus, middle frontal gyrus, superior frontal gyrus, cingulate gyrus, parahippocampal gyrus, thalamus, lentiform nucleus, caudate and substantia nigra.

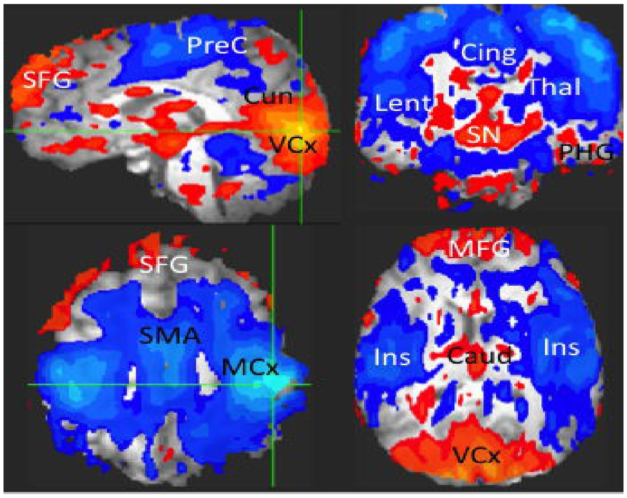

Figure 3: Sensory subnetwork (orange) and motor subnetwork (blue) Cross marks denote positions where signal-intensity time courses for sensory input (top) and motor output (bottom) were extracted. Abbreviations as in figure 2, in addition: PreC: precuneus, SN: substantia nigra.

In contrast, brain regions which exhibited a stronger interaction (synchrony) with the signal-time course of the motor cortex were bilateral post central gyrus, supplementary motor area (SMA), precentral gyrus, middle frontal gyrus, insula and regions in the cerebellum (figure 3).

C. *Quantification of Interaction Strength*

The percentages of interactions involving the visual cortex ranged from 85 % (subject 4) to 18 % (subject 1), average: 46 ±23 % and the motor cortex ranged from 40 % (subject 3) to 9 % (subject 1) average 21 ± 11 %. Other regions with high interactions were: frontal cortex (19 ± 18 %), insula (17 ± 22 %), cuneus (16 ± 15 %), SMA (11 ± 18 %) and several subcortical regions including the thalamus, the lentiform nucleus and the caudate (11 ± 10 %).Interactions between motor cortex, SMA and visual cortex accounted for 12 %, between visual cortex and cuneus for 8 % and between motor cortex, SMA and cuneus for 6 % of all interactions. These quantitative findings are supported by the visual impressions from the 2D and 3D network layouts (figures 4 and 5).

IV. DISCUSSION

We hypothesize the following model of neural activity during the generation of willed behavior in approach/avoidance situations: The perception of an external stimulus is evaluated against prior experience (memory), evoking a visceral-motor response (emotion). Visceral motor regions activate motor areas that execute a behavioral response appropriate to the well-being of the organism. To test this hypothesis, we have developed the behavioral paradigm and the graph-theoretical analysis of the fMRI BOLD activation maps as described above, to identify the brain regions involved and the sequence of their activation. Sporns et al. in a recent review article have emphasized the potential of the human connectome 'a comprehensive structural description of the network elements and connections forming the human brain' [5]) as a theoretical foundation for cognitive neuroscience. In the framework of the human connectome, the methodologies presented in this paper were developed to understand the brain areas involved in the execution of the introduced paradigm (MCODE cluster analysis) and to understand their hierarchical interplay (GC analysis). Graph-theoretical network concepts are increasingly used in biology, genetics and neuroscience [6]. Early studies used connectivity measures derived from neuroanatomical investigations to create network description of the brain of non-human primates [7]. Results indicated that the cerebral cortex is composed of clusters of densely and reciprocally coupled cortical areas [8]. Recent reports on the connectivity of white matter fibers obtained from magnetic resonance diffusion spectrum imaging confirmed and expanded these early findings [9]. The structural composition of the functionally active brain regions obtained with the MCODE analysis presented in this work are in good agreement with the findings reported in the literature: a small-world network structure was found where voxels with synchronized intensity time-courses form distinct clusters.

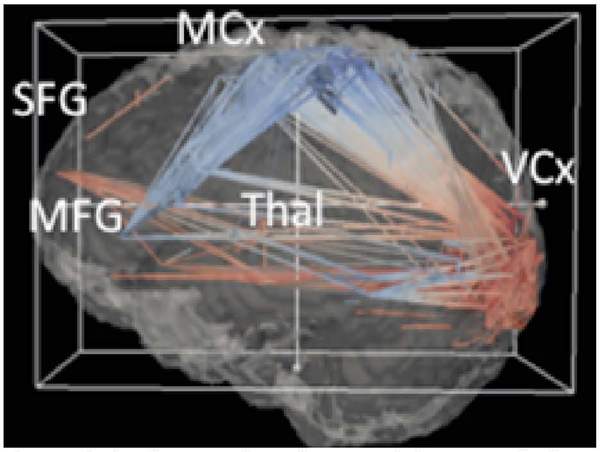

Figure 4: 3D layout of graph network in anatomical space for subject 9. Edges connect nodes of the sensory subnetwork (orange) and the motor subnetwork (blue)..

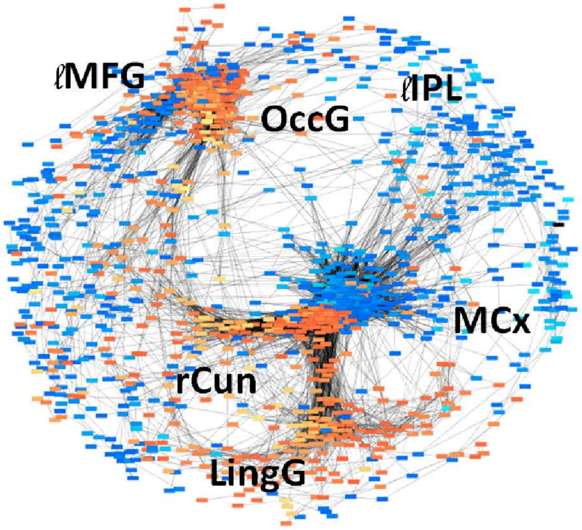

Figure 5: Same network as shown in figure 4 in a spring-embedded layout (cytoscape). Abbreviations as in figure 3

While the temporal resolution of our fMRI study has to be considered large for resolving temporal events during the initiation of the willed motor response, our approach allows us to identify brain regions that interact during this process. We find variable interaction strengths between the sensory subnetwork and the motor subnetwork in our subjects. These results suggest an individual variability in the response to the presented stimulus, i.e. the emotional motivation for initiating the motor response. Our choice of the voxel-intensity time courses for the visual cortex (visual input) and motor cortex (motor output) will also influence the here presented results. We believe this to be an effect of second order: while the exact shapes of the time courses will alter the correlation coefficient values slightly, the presence of visual stimulus for every face and the presence of a motor output for each unpleasant face only, will dominate the correlation strength. We are in the process of integrating EEG recordings using an fMRI-compatible EEG system to resolve temporal events during the execution of the paradigm to be able to add temporal information to the emerging pattern of functional connectivity presented here.

V. CONCLUSION

During the execution of an approach-avoidance paradigm, strong interaction of the visual cortex either directly or via the cuneus with the motor cortex and SMA and subcortical regions including thalamus, lentiform nucleus and substantia nigra was found utilizing graph-theoretical analysis techniques.

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