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Graph Theoretical Connectivity Analysis of the Human Brain while Listening to Music with Emotional Attachment: Feasibility Study*

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Abstract— **Benefits of listening to music with emotional attachment while recovering from a cerebral ischemic event have been reported. To develop a better understanding of the effects of music listening on the human brain, an algorithm for the graph-theoretical analysis of functional magnetic resonance imaging (fMRI) data was developed. From BOLD data of two paradigms (block-design, first piece: music without emotional attachment, additional visual guidance by a moving cursor in the score sheet; second piece: music with emotional attachment), network graphs were constructed with correlations between signal time courses as edge weights. Functional subunits in these graphs were identified with the MCODE clustering algorithm and mapped back into anatomical space using AFNI. Emotional centers including the right amygdala and bilateral insula were activated by the second piece (emotional attachment) but not by the first piece. Network clustering analysis revealed two separate networks of small-world property corresponding to task-oriented and resting state conditions, respectively. Functional subunits with highest interactions were bilateral precuneus for the first piece and left middle frontal gyrus and right amygdala, bilateral insula, left middle temporal gyrus for the second piece. Our results indicate that fMRI in connection with graph theoretical network analysis is capable of identifying and differentiating functional subunits in the human brain when listening to music with and without emotional attachment.**

I. Introduction

Music is one of the most powerful stimuli for the human brain, it triggers a complicated sequence of cognitive and emotional responses [1]. Neural activity associated with music listening not only involves the auditory cortex but a complex network including regions in both brain hemispheres. Many of these regions are also recruited for attention, memory and motor functions [2]. Other regions located in the limbic system are known to participate in emotional processing [3]. When recovering from stroke, the human brain is capable of large plastic changes [4]. Elements of music have been explored for applications in stroke rehabilitation as part of physiotherapy [5]. A large number of studies have demonstrated that environmental stimuli can influence these changes and enhance recovery [6]. Animal studies have hinted of enhancement of memory functions in rats [7] in a music compared to a noise environment. A recent single-blind, controlled trial [8], randomized 60 patients with a left or right hemisphere middle cerebral artery stroke to a music group, a language group, or a control group. Results showed that recovery in the domains of verbal memory and focused attention improved significantly more in the music group than in the language and control groups. The music group also experienced less depression and confusion than the control group. The effect of music with emotional attachment for musical therapy is not well understood but might be of great importance for the efficacy of music therapy by triggering pleasant memories. We hypothesize it will active emotional brain centers. To demonstrate the feasibility of identifying functional subunits in the brain while listening to music which evokes emotions, we performed a pilot study with one healthy volunteer listening to music without any emotional attachment (piece 1) and to music attached to strong pleasant memories (piece 2) using a graph-theoretical network analysis approach.

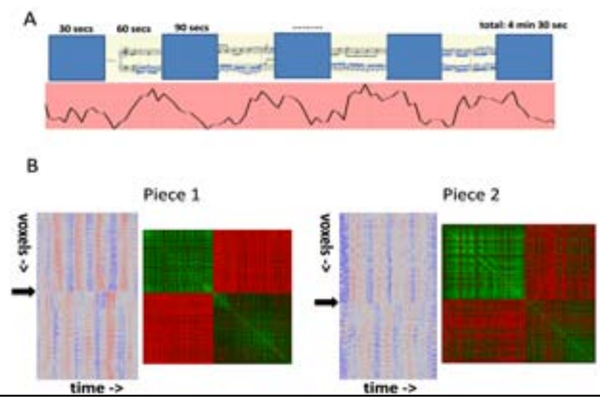

Figure 1: A: Illustration of the block design. Periods of music listening (score sheets) are interleaved by rest (blue). **B:** BOLD-intensity time courses (on left, red: positive signal change, blue: negative signal change) and correlation matrices (on right: green: positive correlation, red: negative correlation) for both pieces.

II. Materials and Methods

A. fMRI Paradigm

Approval of the Institutional Review Board was obtained for this study. One healthy subject (42 years, male, musician and composer, 20 years of training and experience) listened to two music pieces in a block-design paradigm (Siemens Verio 3T whole body human scanner, Siemens Medical Solutions, Erlangen, Germany, fMRI equipment by Nordic NeuroLab Inc):

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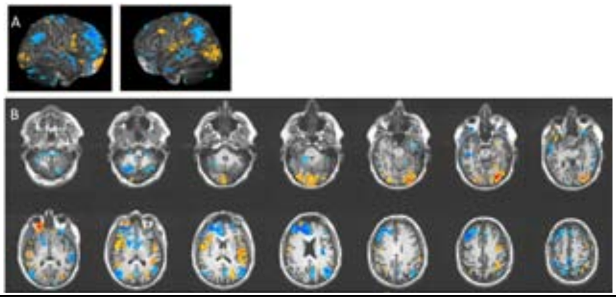

Figure 2: A and **B:** fMRI BOLD activation maps (orange: active, blue: rest) for piece 1 (no emotional attachment, visual and auditory stimulation).

In the first paradigm, the subject listened to a music piece without emotional attachment (Bach invention #1) in a block-design manner: the music was paused every 30 seconds for 30 seconds (4 repetitions, figure 1a). In addition, a visual display showed the score sheet and a moving cursor indicating the location of the notes heard by the subject at a given time. In the second paradigm, the subject listened to a music piece (Two Silver Hearts by Shake Russell) using the same block-design. According to his own statement, the subject had strong pleasant memories of this music piece. Axial slices (echo planar imaging, echo time TE=30 ms, repetition time TR=3000 ms, field of view FOV= 240 mm x 240 mm, acquisition matrix 32x64 resulting in an interpolated in-plane resolution of 3.3 mm) were acquired of the entire brain. A high-resolution anatomical scan was acquired as well. Individual fMRI activation maps (AFNI, via the general linear model) 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).

B Network Analysis

For each paradigm, voxel-intensity time-courses were extracted for the 40 % of all voxels with the highest z-scores in the fMRI activation map. Employing the R statistical language, network adjacency matrices were defined as the correlation matrices for voxel-intensity time-courses (discarding any correlation coefficient (CC) value lower than 0.8, figure 1b). The particular values for the z-score threshold and the CC cut-off were identified from a sensitivity analysis (data not shown). The adjacency matrices were converted into the Graph modeling language (gml) using the 'igraph' library for R (igraph.sourceforge.net) and imported into Cytoscape (version 2.8.1, www.cytoscape.org) for graph-theoretical analysis as follows: Spring-embedded layouts were created to obtain a qualitative visual impression of the network. Then, selected network parameters were calculated with the Cytoscape 'Network Analysis' plugin including the clustering coefficient (fraction of connections (out of all possible) that connect the neighbors of a given node), the characteristic path length (average of all distances in a network) and the network heterogeneity. The latter parameter is based on the variance of connectivity of all nodes and reflects the tendency of a network to contain hub nodes [9] and is of particular

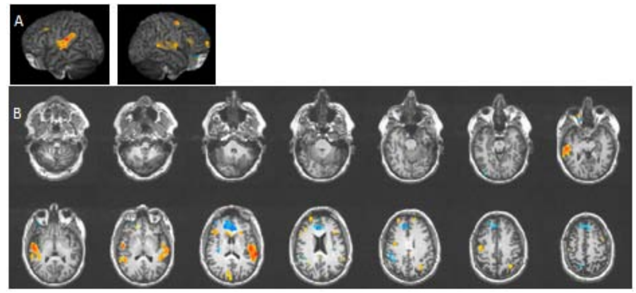

Figure 3: A and **B**: fMRI BOLD activation maps (orange: active, blue: rest) for piece 2 (emotional attachment, auditory only stimulation).

interest as brain networks have previously been shown to exhibit a small-world structure [10]. To further investigate the small-world nature of the graph networks for both paradigms, values for the correlation coefficient and characteristic path length were compared with random networks generated with the Barabasi-Albert model constructed having the same number of nodes.

C Graph-Theoretical Cluster Analysis

To separate the whole network into individual clusters, the Molecular Complex Detection (MCODE) algorithm [11] as implemented in the Cytoscape ClusterViz plugin was employed. Time courses for each cluster were calculated by averaging the time courses of all voxels belonging to each cluster and using correlation analysis, interaction strengths for cluster pairs were determined and graph adjacency matrices calculated and visualized. For illustration purposes, the 10 highest interactions were displayed as network graphs.

III. RESULTS

A. fMRI Activation Maps

More brain regions with BOLD activation and resting activation were found for piece 1 (no emotional attachment, auditory and visual guidance) compared to piece 2 (emotional attachment, auditory only). For the first piece, regions activated included the bilateral occipital lobes, bilateral auditory cortex, bilateral precuneus, left inferior frontal, left transverse temporal, left cuneus, and right postcentral gyrus (figure 2 a,b). Regions activated during the resting part of the paradigm (resting state) included right superior, medial and middle frontal gyrus, right lentiform nucleus, left inferior parietal gyrus and left precuneus. For piece 2, BOLD activation during listening included bilateral auditory cortex, bilateral inferior and superior parietal lobule, bilateral insula, bilateral precuneus, left inferior frontal gyrus, left superior and middle temporal gyrus and left inferior and middle frontal gyrus. Resting activation was found in the left angular and left middle temporal, the right medial frontal and postcentral gyrus and the right inferior parietal lobule (figure 3 a,b).

B. Network Analysis

For both pieces, separate networks composed either of brain regions with increased BOLD signal during the listening periods or during the resting periods were found (figure 4). While for piece 1 the network graph for brain

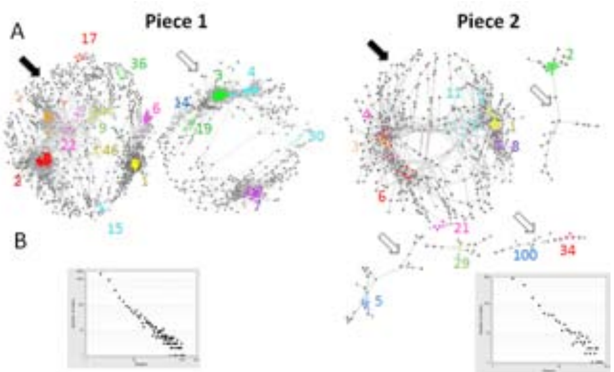

Figure 4: A: Spring-embedded display of networks for brain regions active during the listening periods of the paradigm (closed arrows) and active during the rest periods (open arrows) for both pieces. Functional subunits (clusters) identified with MCODE are shown in color and numbered descending by size. **B:** Double logarithmic plot of network node-degree distribution indicating small-world nature of the functional networks in A.

regions active during rest resembled the one for the brain regions active during music listening, for piece 2, the resting state network was fragmented into 5 sub-networks. Network graph for piece 1 contained more than double the number of nodes and more than three times the number of edges than the one for piece 2. Clustering coefficient, network heterogeneity and characteristic path length were all elevated for piece 1 compared to piece 2 (table 1). Shape of double logarithmic plot of node degree distribution was linear indicating a scale-free network

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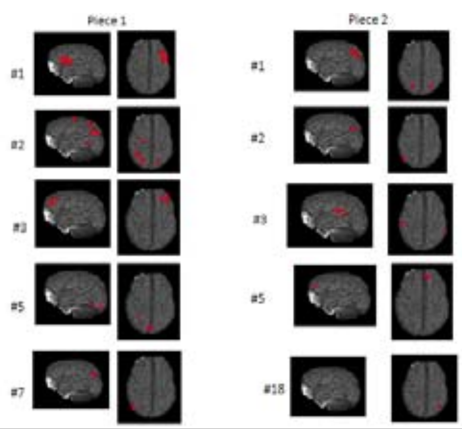

Figure 5: Anatomical location of voxels belonging to selected functional sub-units (clusters) identified as numbered as in figure 4a.

Values for correlation coefficients compared to the ones for random networks generated with the Barabasi-Albert model were distinctly high and characteristic network lengths were comparable (table 1) emphasizing the small-world structure of the network graphs.

C. Graph-Theoretical Cluster Analysis

Largest clusters in general corresponded to locations in the network graph that visually appeared dense (figure 4) and corresponded to two categories: either one or several highly localized distinct anatomical regions when mapped back into anatomical space (figure 5). The largest anatomical clusters for piece 1 and the second-largest cluster for piece 2, examples of the first category, were located in the right inferior parietal lobe and the left angular gyrus, respectively. The second-largest cluster for piece 1, located in the left and right inferior and superior parietal lobule, and the largest cluster for piece 2, located in the left and right precuneus, left superior parietal lobule and left middle temporal gyrus, the are examples of the second category (figure 5). Of note is the presence of an 'emotional cluster' for piece 2 consisting of right amygdala, bilateral insula and left middle temporal gyrus, i.e. containing brain regions involved in emotional processing and potential memory retrieval. A similar cluster was absent for piece 1.

TABLE I. NETWORK PARAMETERS

Network Parameters	*Piece 1*	*Piece 2*
Number of nodes	4,026	1,709
Number of edges	15,557	4,104
Clustering coefficient (values for Barabasi-Albert model in parenthesis)	0.201 (0.012)	0.148 (0.029)
Characteristic path length	6.501 (4.571)	5.245 (4.232)
Network heterogeneity	2.373	1.973

Largest clusters corresponding to dense regions in the network graphs (n=16 for paradigm 1 and n=12 for paradigm 2) were used to calculate a correlation matrix (adjacency matrix) for cluster interaction and, focusing on the 10 highest interactions, cluster-interaction networks strength were quantified (correlation analysis). For piece 1, this cluster interaction networks consisted of two separate networks with clusters either belonging to brain regions active during listening or active during rest. The cluster interaction network for piece 2 consisted mainly of clusters corresponding to active brain region while listening with the exception of one cluster that corresponded to a resting state brain region in the right postcentral gyrus which showed a high interaction strength with the 'emotional cluster '. For piece 1, a cluster comprising voxels in the bilateral precuneus showed highest interaction with other functional subunits. For piece 2, a cluster comprised of voxels in the left middle frontal and left inferior parietal lobe showed highest interaction strengths followed by 'the emotional cluster'.

IV. DISCUSSION

With the aid of a data-driven graph-theoretical network approach, differences in the interaction strength of distinct brain regions were quantified when listening to music with emotional attachment. The role of the inferior frontal gyrus is thought to participate in music-syntactic analysis [12]. Both music pieces solicited activation in the inferior frontal gyrus with larger activation for the first piece. We speculate that visual presentation of the music score including the moving cursor may have enhanced syntactic processing. Listening to the second piece activated the right amygdala. The amygdala plays a key role in emotional processing and limited evidence suggests that the right amygdala is involved in automatic evaluation of emotions while the left amygdala processes conscious and cognitive controlled emotions [13]. Music with no emotional attachment did not activate the amygdala, hinting at a difference in emotional processing. Activation patterns at rest for both pieces included medial frontal and parietal regions which have previously been identified to be part of the Default Mode Network or resting state network of the brain [14]. The graph-theoretical analysis identified scale-free, small-world structured networks similar to brain networks derived from anatomical connectivity [15]. Clusters or functional subunits were identified with the MCODE algorithm. For piece 1, the visual cortex contained the cluster with highest degree followed by the precuneus, thereby emphasizing the already established role of the precuneus as one of the brain regions with highest connectivity [16]. For paradigm 2, an 'emotional cluster', comprising regions of emotional processing, had the highest degree. The goal of the here presented study was to demonstrate the feasibility of network-graph analysis for deriving brain activation maps for both paradigms as well as for indentifying functional subunits in the brain and quantifying their interactions in music listening. The derived algorithms can be transferred easily to a larger group of subjects and a more general distinction between both paradigms can then be analyzed in a similar matter.

V. Conclusion

Music with emotional attachment and music without emotional attachment may affect subjects undergoing music therapy differently by activating different brain centers. Here, we present a paradigm and analysis concept that is capable of identifying functional subunits and their interaction strengths. The here presented methodology may used to image and quantify changes occurring in functional activation of the brain of patients undergoing musical therapy

References

[1] I. Peretz and R. J. Zatorre, "Brain organization for music processing," *Annu Rev Psychol,* vol. 56, pp. 89-114, 2005.

[2] P. Janata, B. Tillmann, and J. J. Bharucha, "Listening to polyphonic music recruits domain-general attention and working memory circuits," *Cogn Affect Behav Neurosci,* vol. 2, pp. 121-40, Jun 2002.

[3] S. Koelsch, T. Fritz, V. C. DY, K. Muller, and A. D. Friederici, "Investigating emotion with music: an fMRI study," *Hum Brain Mapp,* vol. 27, pp. 239-50, Mar 2006.

[4] S. H. Kreisel, M. G. Hennerici, and H. Bazner, "Pathophysiology of stroke rehabilitation: the natural course of clinical recovery, use-dependent plasticity and rehabilitative outcome," *Cerebrovasc Dis,* vol. 23, pp. 243-55, 2007.

[5] M. H. Thaut, G. C. McIntosh, and R. R. Rice, "Rhythmic facilitation of gait training in hemiparetic stroke rehabilitation," *J Neurol Sci,* vol. 151, pp. 207-12, Oct 22 1997.

[6] F. C. Hummel and L. G. Cohen, "Drivers of brain plasticity," *Curr Opin Neurol,* vol. 18, pp. 667-74, Dec 2005.

[7] H. Kim, M. H. Lee, H. K. Chang, T. H. Lee, H. H. Lee, M. C. Shin, M. S. Shin, R. Won, H. S. Shin, and C. J. Kim, "Influence of prenatal noise and music on the spatial memory and neurogenesis in the hippocampus of developing rats," *Brain Dev,* vol. 28, pp. 109-14, Mar 2006.

[8] T. Sarkamo, M. Tervaniemi, S. Laitinen, A. Forsblom, S. Soinila, M. Mikkonen, T. Autti, H. M. Silvennoinen, J. Erkkila, M. Laine, I. Peretz, and M. Hietanen, "Music listening enhances cognitive recovery and mood after middle cerebral artery stroke," *Brain,* vol. 131, pp. 866-76, Mar 2008.

[9] J. Dong and S. Horvath, "Understanding network concepts in modules," *BMC Syst Biol,* vol. 1, p. 24, 2007.

[10] P. Hagmann, L. Cammoun, X. Gigandet, R. Meuli, C. J. Honey, V. J. Wedeen, and O. Sporns, "Mapping the structural core of human cerebral cortex," *PLoS Biol,* vol. 6, p. e159, Jul 1 2008.

[11] G. D. Bader and C. W. Hogue, "An automated method for finding molecular complexes in large protein interaction networks," *BMC Bioinformatics,* vol. 4, p. 2, Jan 13 2003.

[12] E. Brattico, V. Alluri, B. Bogert, T. Jacobsen, N. Vartiainen, S. Nieminen, and M. Tervaniemi, "A Functional MRI Study of Happy and Sad Emotions in Music with and without Lyrics," *Front Psychol,* vol. 2, p. 308, Dec 2011

[13] D. Baas, A. Aleman, and R. S. Kahn, "Lateralization of amygdala activation: a systematic review of functional neuroimaging studies," *Brain Res Brain Res Rev,* vol. 45, pp. 96-103, May 2004.

[14] R. L. Buckner, J. R. Andrews-Hanna, and D. L. Schacter, "The brain's default network: anatomy, function, and relevance to disease," *Ann N Y Acad Sci,* vol. 1124, pp. 1-38, Mar 2008.

[15] O. Sporns, D. R. Chialvo, M. Kaiser, and C. C. Hilgetag, "Organization, development and function of complex brain networks," *Trends Cogn Sci,* vol. 8, pp. 418-25, Sep 2004.

[16] S. Zhang and C. S. Li, "Functional connectivity mapping of the human precuneus by resting state fMRI," *Neuroimage,* vol. 59, pp. 3548-62, Feb 15, 2012