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Electrophysiological characteristics of age-related changes in cognitive processes related to arithmetic operations

Summary of the doctoral (PhD) dissertation

Supervisor: Dr. Márk Molnár, DSc.

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1 ABSTRACT

During mental arithmetic operations (working) memory plays an important role, but there are only a few studies in which an attempt was made to separate this effect from the process of arithmetic itself and to study the effects of healthy aging on these mental operations. In the present study the effects of mental arithmetic was investigated on the EEG in young and elderly adults during an addition and a subtraction task in the theta (4-8 Hz) frequency band. Besides the power density spectrum analysis, recently developed graph theoretical methods were used and graph topological descriptors (the cluster coefficient: corresponding to the strength of local connections, and global interconnectedness of network: revealed by the path length) and indices of minimal spanning trees and modules (betweenness centrality, degree, diameter, eccentricity, number of leafs) based on phase synchrony (phase lag index, PLI) were determined. Before the arithmetic tasks passive viewing (control condition) and number recognition paradigms were used. The changes during the addition and extraction paradigms were similar. Higher theta power and phase synchronization were found in the young during most task types. Furthermore, network parameters of these conditions showed small world characteristics in the young, but not in the elderly. The shift of network organization towards random topology observed in the elderly group could be the effect of extensive resource compensation mechanisms which has been described earlier in the literature. The integration of the networks was reduced as a consequence of aging; task dependent PLI (which increased with increased task difficulty) and PLI based graph parameter changes were found in all brain regions. The changes of these variables observed in the number recognition task and that of the effect of difficulty of the task seen in the elderly were opposite to those seen in the young. These results are consistent with current relevant applicable theories and may be explained by the deficit which caused by natural aging processes that occur during memory tasks and may correspond to compensation mechanisms elicited by higher workload. Frontal, task relevant synchronization was found by using different methods, in addition to which increased occipital synchronization was observed by a number of indices which may be the result of operations with using Arabic numerals. It was also shown that the method of minimal spanning trees provided an objective (threshold free) and suitable framework for objective analysis of task motivated reorganization of brain areas. The use of our self-developed visualization processes allowed the optimal way of interpretation of these results. The analysis of brain electrical activity by up-to-date graph theoretical approach was used in this dissertation to enable the study the organization of human brain and its changing communication abilities with respect to cognitive functions during healthy aging. Based on this approach, we were able to map the structure of different brain networks It was possible to identify regions the role of which became more fundamental and those which became less important due to the aging process, and to illustrate our results clearly with a new method.

2 RESEARCH QUESTIONS OF THE THESIS

2.1 ADDITION

Q1- The arithmetic operations include the short-term memory maintenance of numbers and cognitive manipulation on the representation of numbers. We assumed that the electrophysiological correlates of memory maintenance and those of corresponding to manipulation of the counting process itself can be separated. We compared the electrophysiological correlates of a standard task (passive viewing of number stimuli), a short-term memory- (maintenance of numbers) task and a mental addition task. In the mental addition task operations were carried out on one-digit numbers, and the outcome was a two-digit number.

Q2- According to our hypothesis the arithmetic processes associated with neural mechanisms of aging - regardless of the difficulty of the task - are less effective, also reflected by the declining behavioral performance. Since these changes may not be reflected merely by increased or a decreased values of certain indices and their spatial distribution can be also informative, we assumed the existence of regionally differently distributed system in the elderly compared to the young, where in addition task-relevant frontal areas the parietal and probably occipital regions will also be involved in task execution. Therefore, several methods were used to analyze our data, and different (frontal, central, temporal, parietal, occipital) brain regions were all investigated depending upon the method used.

2.2 SUBTRACTION

Q3- Similarly to the addition task, it was hypothesized that the different components of the memory task and those of the counting process can be separated. Accordingly, the electrophysiological correlates of viewing a series of stimuli (no task condition) and those corresponding to a purely memory load condition and those corresponding to mental arithmetics were compared to be able to verify this assumption. In this mental arithmetic task operations were carried out on two-digit numbers, and the outcome was also a two-digit number.

Q4- Similarly the addition task, age related, area-specific changes were assumed to take place during the performance of this arithmetic task, regardless of its difficulty. Based on the former study, the topological information was analyzed in the frontal, central, temporal, parietal, occipital brain regions, where it was allowed by the methods used.

2.3 QUESTIONS REGARDING TO BOTH TYPES OF ARITHMETIC OPERATIONS

Q5- Application of graph theory has become an increasingly widespread practice in neuroscience and the "small world" organization of the brain has been discussed by numerous studies. In addition to these earlier studies the need to develop an appropriate, method that is capable to handle well-known difficulties such as threshold selection and does not rely on various other subjective factors (such as selection of calculation parameters) , but can effectively explore the task- and/or group-specific (re)organization of the brain. According to our assumption the method of minimum spanning trees (MST) is suitable for this purpose: To be able to test this, the results obtained by the application of MST were compared with those obtained by the use of conventional methods (power spectral density and PLI).

Q6- By the application of the MST method the complete description of the dynamic operation of complex networks can be achieved (e.g. proportion of leafs, neighborhood relations, regional rates, hubs and other upgraded nodes). Similarly to the necessity to avoid subjective factors to play a role in the calculation process the ability to visualize the changes of these parameters (variables?) is also important Accordingly, we examined how an MST can be shown so that the above aspects can be well distinguished and we have developed two methods that allow all important information of the MST to be displayed.

Reorganization of various age- and task specific frontal-occipital networks were found corresponding to the tasks investigated. The main results related to the different types of mental arithmetic operations are summarized in the following tables. These are the results obtained in the young group of participants (Table 1), the results of the elderly group (Table 2), and the results of the elderly in comparison with the young (Table 3), respectively.

<table>
<tr><th>young participants</th><th>type of task</th><th>task compared to passive viewing</th><th>task compared to number recognition</th></tr>
<tr><td rowspan="2">power spectral density</td><td>addition</td><td colspan="2">higher theta power in the left side</td></tr>
<tr><td>subtraction</td><td colspan="2">similar results</td></tr>
<tr><td rowspan="2">PLI</td><td>addition</td><td colspan="2">higher PLI</td></tr>
<tr><td>subtraction</td><td colspan="2">higher PLI</td></tr>
<tr><td rowspan="2">cluster coefficient</td><td>addition</td><td colspan="2">higher C</td></tr>
<tr><td>subtraction</td><td colspan="2">higher C</td></tr>
<tr><td rowspan="2">path length</td><td>addition</td><td colspan="2">shorter path length</td></tr>
<tr><td>subtraction</td><td colspan="2">shorter path length</td></tr>
<tr><td rowspan="2">BC</td><td>addition</td><td>lower BC</td><td>similar results</td></tr>
<tr><td>subtraction</td><td colspan="2">similar results</td></tr>
<tr><td rowspan="2">degree</td><td>addition</td><td colspan="2">higher degree</td></tr>
<tr><td>subtraction</td><td colspan="2">similar results</td></tr>
<tr><td rowspan="2">diameter</td><td>addition</td><td colspan="2">smaller diameter</td></tr>
<tr><td>subtraction</td><td>smaller diameter</td><td>similar results</td></tr>
<tr><td rowspan="2">eccentricity</td><td>addition</td><td colspan="2">decreasing eccentricity</td></tr>
<tr><td>subtraction</td><td>decreasing eccentricity</td><td>similar results</td></tr>
<tr><td rowspan="2">proportion of leafs</td><td>addition</td><td colspan="2">increasing proportion of leafs</td></tr>
<tr><td>subtraction</td><td colspan="2">increase with the complexity of task</td></tr>
</table>

TABLE 1

elderly participants	*type of task*	*task compared to passive viewing*	*task compared to number recognition*
power spectral density	***addition***	higher theta power in occipital lobe	
	subtraction	higher theta power in occipital region	
PLI	***addition***	similar results	higher PLI
	subtraction	similar results	higher PLI
cluster coefficient	***addition***	similar results	higher C
	subtraction	similar results	higher C
path length	***addition***	shorter path length	
	subtraction	similar results	shorter path length
BC	***addition***	similar results	lower BC
	subtraction	similar results	
degree	***addition***	higher degree	
	subtraction	similar results	higher degree
diameter	***addition***	similar results	smaller diameter
	subtraction	similar results	smaller diameter
eccentricity	***addition***	decreasing eccentricity	
	subtraction	similar results	decreasing eccentricity
proportion of leafs	***addition***	increasing proportion of leafs	
	subtraction	increasing independently from the complexity of task	

TABLE 2

<table>
<tr><th>young compared to elderly</th><th>type of task</th><th>task</th><th>passive viewing and number recognition</th></tr>
<tr><td rowspan="2">power spectral density</td><td>addition</td><td colspan="2">higher theta power</td></tr>
<tr><td>subtraction</td><td colspan="2">higher theta power</td></tr>
<tr><td rowspan="2">PLI</td><td>addition</td><td>higher PLI</td><td>significantly lower PLI in the number recognition in the elderly</td></tr>
<tr><td>subtraction</td><td colspan="2">higher PLI in occipital lobe, similar results in groups</td></tr>
<tr><td rowspan="2">cluster coefficient</td><td>addition</td><td>similar results</td><td>significantly lower C in the number recognition in the elderly</td></tr>
<tr><td>subtraction</td><td>higher C</td><td>significantly lower C in the number recognition in the elderly</td></tr>
<tr><td rowspan="2">path length</td><td>addition</td><td>similar results</td><td>significantly longer L in the number recognition in the elderly</td></tr>
<tr><td>subtraction</td><td>shorter path length</td><td>significantly longer L in the number recognition in the elderly</td></tr>
<tr><td rowspan="2">BC</td><td>addition</td><td colspan="2">higher occipital BC in both groups</td></tr>
<tr><td>subtraction</td><td colspan="2">higher occipital BC in both groups</td></tr>
<tr><td rowspan="2">degree</td><td>addition</td><td colspan="2">higher degree in frontal-occipital areas in both groups</td></tr>
<tr><td>subtraction</td><td colspan="2">higher degree in frontal-temporal- occipital areas in both groups</td></tr>
<tr><td rowspan="2">diameter</td><td>addition</td><td>similar results</td><td>moderate larger diameter in the number recognition in the elderly</td></tr>
<tr><td>subtraction</td><td>similar results</td><td>moderate larger diameter in the number recognition in the elderly</td></tr>
<tr><td rowspan="2">eccentricity</td><td>addition</td><td>similar results</td><td>moderate larger eccentricity in the number recognition in the elderly</td></tr>
<tr><td>subtraction</td><td>similar results</td><td>moderate larger eccentricity in the number recognition in the elderly</td></tr>
<tr><td rowspan="2">proportion of leafs</td><td>addition</td><td>similar results</td><td>increasing proportion of leafs in the number recognition in the elderly</td></tr>
<tr><td>subtraction</td><td>similar results</td><td>no change with the complexity of task in the elderly</td></tr>
</table>

TABLE 3

4.1 ADDITION

Q1 Higher relative spectral power was found in left in theta band during the addition task than in the right side. Compared to the control and number recognition cognitions higher C and lower L, and with respect to the MST parameters shortening diameter and paths and more leafs were found in both groups. Changes of the various parameters were characteristic of the different analyzed conditions which were more likely the correlates of mental arithmetics and not of memory retention. Deficits in several parameters (such as power spectra, PLI, C, L) were found in the elderly in the number recognition task, which compared to the passive control and the addition task on the one hand, and compared to the number recognition task in the young on the other hand corresponds age related memory decline.

Q2 Higher theta power was found in the addition and in the number recognition tasks in the young than in the elderly, and higher theta power was found in the elderly in these two tasks in the occipital region than in other brain areas. Higher levels of PLI were observed in all analyzed conditions in the young than in the elderly, but – contrary to that seen in the young - significant decrease was found in the number recognition task compared to the passive and the arithmetic tasks. Lower C and higher L values were found the elderly compared with the young. With respect to the main effect of age the value of C was found to be lower, that of L was found to be higher in the elderly group. Also in the elderly group a tendency of lower C and higher L was observed corresponding to the number recognition task compared to that found in the two other tasks. A similar trend was found for the MST parameters (significantly lower BC and increased diameter and distance were found during the number recognition task compared to addition), which suggests that healthy aging is accompanied by memory deficits, while the ability to perform arithmetic operations –due to the involvement of more extended regional activation – may still be retained.

4.2 SUBTRACTION

Q3 Higher PLI, C and lower L were found in the subtraction task in both groups in the theta band. With respect to MST parameters smaller diameter, shorter routes and growing number of letters were found in the subtraction situation. Based on the results of this analysis the passive viewing and number recognition conditions could not be differentiated from each other although - similarly to the addition task- trends related to the difficulty of the task were also found in this analysis. It was concluded that the corresponding changes were likely to be associated with subtraction evoked activity and not to memory maintenance.

Q4 Higher theta power was found in the young during the subtraction task, which appeared as a main effect of age, and higher occipital theta power was observed in the elderly compared to other regions. Lower PLI values were found in the subtraction task in the elderly than in the young. Significantly lower PLI was found in the elderly during number recognition than subtraction. Lower C and higher L values were found in the elderly than in the young and significantly lower C and higher L were found corresponding to the number recognition task compared to the subtraction task in this group. A decreasing number of degrees, increasing diameter and eccentricity were found in the MST parameters in the number recognition task compared to subtraction in the elderly. The main effect of healthy aging on decreasing theta power and synchronization – as a statistically main effect - is well known in the literature. Similarly to the results of the addition tasks the observed deficit of memory recall task was found here as well, so it is likely that the effects of the aging can be detected by the investigation of these functions.

4.3 QUESTIONS RELATED TO OF BOTH TYPES OF TASKS

Q5 Compared to the C and L parameters that have been already studied earlier, the analysis of MSTs can eliminate the subjective threshold selection problem, and is not only comparable to PLI results, but is also capable to add new information concerning the hierarchical organization of the brain as well. The results of the analysis of separated and interconnected nodes appears only in an indirect way in PLI data – shown with respect to different regions in the present dissertation – but the use of MST, in addition to the investigation of the strongest connections allows also to study the size and intensity of connectivity network of certain areas during the performance of various tasks. In addition to the above the most important yield provided by the use of MST was the possibility to show important correlations which was possible only by the application of a number of other methods. No previously used method has shown such sensivity for all the observed changes; power spectrum for example does not provide information concerning the connectivity of different regions and PLI results do not shed light on the pattern of most important regional connectivities either. The important role of the occipital area was showed by considering BC in addition task and also in the subtraction task. The difficulty of task could be sensitively detected by the degree in the addition task, while intensifying connectivity in the frontal, temporal, occipital areas were marked by this parameter in the subtraction task. Based on these findings, this indicator may be appropriate to separate these two types of mental calculations. The changes that occur in brain networks can be well described by determining the diameter, eccentricity and the ratio of leafs. The changes found in all of these indices support the "small world" type of transformation in the brain during increasingly difficult tasks.

Q6 MSTs may be plotted as simple graphs, but a new solution was developed by our research group for their display showing spatial, topological and connectivity information as well. BC showed occipital upgrading and the degree appeared to be capable to differentiate the two basic types of arithmetic operations. Together with diameter, diameter, eccentricity and ratio of leafs it changed in proportion with task difficulty tracking correctly the fronto-temporo-occipital transformation of brain networks. All these changes can be displayed by the specifically developed software of Bálint File (File et. al., 2012), resulting in a transparent graph structure similar to the traditional mapping (scalp distribution of nodes are shown with edges running between them). These plots are well supplemented by the results of our co-operatively developed software which allows the display of the data in the traditional MST format (without scalp distribution). In addition to electrode identification the area codes, connected groups (with their strength) and the busiest hubs can also be found in these MST plots (File et. al., 2012).

5 LIST OF PUBLICATIONS RELATED TO DISSERTATION

5.1 JOURNAL ARTICLES

Boha, R., Tóth B., Gaál, Zs. A., Kardos, Zs., File, B., Molnár, M. (2013) Számolási teljesítmény spektrális, fázisszinkronizációs és gráfelméleti EEG-jellemzői. *Clinical Neuroscience,* 66:(5-6) pp. 175-183.

Molnár, M., Tóth, B., Boha, R., Gaál, Zs. A. (2012) Érzelmek hatása a válaszgátlásra - Életkori sajátosságok elektrofiziológiai adatok tükrében. *Pszichológia*, 32:(1) pp. 19-36.

Molnár, M., Boha, R., Benyovszky, M., Gaál, Zs. A., Tóth, B. (2011) Öregedés és számolási teljesítmény: Az EEG spektrális, komplexitás- és hálózatjellemzői. *Clinical Neuroscience*, 64:(1-2) pp. 41-49.

Gaál, Zs. A., Boha, R., Stam, C. J., Molnár, M. (2010) Age-dependent features of EEG-reactivity—Spectral, complexity, and network characteristic. *Neuroscience Letters*, 479: pp. 79-84.

Molnár, M., Gaál, Zs. A., Boha, R., Tóth, B., Benyovszky, M., Czigler, B. (2010) Kognitív folyamatok elemzése a neurális komplexitás elektrofiziológiai korrelátumainak alapján. *Magyar Pszichológiai Szemle*, 65:(4) pp. 621-634.

Molnár, M., Boha, R., Czigler, B., Gaál, Zs. A. (2010) The acute effect of alcohol on various memory processes. *International Journal of Psychophysiology,* 24:(4) pp. 249-252.

Boha, R., Molnár, M., Gaál, Zs. A. , Czigler, B., Róna, K., Kass, K., Klausz, G. (2009) The acute effect of low-dose alcohol on working memory during mental arithmetic I. Behavioral measures and EEG theta band spectral characteristics. *International Journal of Psychophysiology*, 73:(2) pp. 133-137.

Molnár, M., Boha, R., Czigler, B., Gaál, Zs. A., Benyovszky, M., Róna, K., Klausz, G. (2009) The acute effect of low-dose alcohol on working memory during mental arithmetic II. Changes of nonlinear and linear EEG-complexity in the theta band, heart rate and electrodermal activity. *International Journal of Psychophysiology,* 73:(2) pp. 138-142.

5.2 CONFERENCE PAPERS

File, B., Tóth, B., Kardos, Zs., Boha, R., Molnár, M. (2013) Source level based investigation of age-related changes in resting state functional connectivity. *Psychophysiology,* 50:(S1) p. S25.

Boha, R., Tóth, B., Gaál, Zs. A. , Molnár, M. (2012) The effect of age on time dependent EEG-synchronization changes during the performance of mental arithmetic task. *International Journal of Psychophysiology,* 85:(3) pp. 429-430.

File, B., Tóth, B., Boha, R., Hidasi, Z., Gaál, Zs.A., Stam, C.J., Molnár, M., (2012) Longitudinal study of resting state functional network characteristics in mild cognitive impairement. *Psychophysiology*, 49, Supplement , pp. S30.

Boha, R., Tóth, B., Gaál, Zs. A., Benyovszky, M., Molnár, M. (2011) Electrophysiological correlates of age-dependent memory processes in mathematical cognition. *13th conference of the Hungarian Neuroscience Society (MITT) Edition,* Frontiers

Boha, R., Tóth, B., Gaál, Zs. A. , Benyovszky, M., Molnár, M. (2010) Age-related correlates of mental arithmetic performance: Changes of EEG-spectra, complexity measures and network characteristics. *International Journal of Psychophysiology,* 77:(3) pp. 258-259.

Molnár, M., Boha, R., Benyovszky, M., Gaál, Zs. A., Tóth, B. (2010) Exhaustion and stress during arithmetic performance - Age-related EEG and ECG characteristics. *International Journal of Psychophysiology,* 77:(3) pp. 219-220.

Boha, R., Benyovszky, M., Gaál, Zs. A. , Tóth, B., Molnár, M. (2009) Age-dependent changes of EEG frequency characteristics and ECG-changes related to working memory processes in arithmetic task connectivity. *Psychophysiology*, 46: p. S35.