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Cognitive dysfunctions associated with white matter damage due to cardiovascular burden – determinants and interpretations

Abstract: Although considerable research has been devoted to cognitive functions deteriorating due to diseases of cardiovascular system, rather less attention has been paid to their theoretical background. Progressive vascular disorders as hypertension, atherosclerosis and carotid artery stenosis generate most of all pathological changes in the white matter, that cause specific cognitive disorder: disconnection syndromes, and disturbances in the dynamic aspect of information processing. These features made neuropsychological disorders secondary to cardiovascular diseases different than the effects of cerebral cortex damage, which may be interpreted modularly.

Key words: hypertension, atherosclerosis, white matter, cognitive processing speed, neural networks

Introduction

This article is concerned with the problem of the neuropsychological disorders secondary to white matter changes in patients with chronic, progressive cardiovascular diseases. The main aim is to explain the etiology of brain changes in patients with cardiovascular burden, to portray its neurocognitive sequels, but primarily to offer relatively deeper understanding of their specific nature.

The text is divided into several sections. The first includes some basic information about cardiovascular system diseases, its epidemiology, classifications, possible impact on brain structures. Next, there are described in more detail selected mechanisms of brain changes secondary to cardiovascular disorders (CVD) and its major cognitive consequences. The article will address the chronic cardiovascular diseases, like hypertension, atherosclerosis and carotid artery occlusion, but not rapidly emerging events, like heart attack or coma due to prolonged heart arrest. The cognitive sequels characteristics also refer mainly to these chronic conditions.

The following parts are devoted to a special type of brain changes secondary to CVD - the white matter lesions (WML) which may be defined as neuropathology of white matter tracts that originates predominantly from ischemic / hypoxic phenomena. These changes are most commonly registered damages in this case. The fact that CVD generate this kind of brain damages forces the necessity to expand theoretical models which would skip the modular explanation. Although the network approach in neuroscience is not new, the neuropsychological interpretations of brain damages, made in accordance with network theories are still rather a niche than the dominant modular way of explanations. In classical neuropsychological studies, authors emphasizes the proper execution of the task, level of correctness, to a lesser extent, the dynamics of the performance. This results in a need to supplement ways of thinking about the cognitive deficits, to understand the specificity of changes in patients with white matter damage.

The models and experimental data are certainly not perfect or final. Given the rapid development of white matter imaging techniques, particularly Diffusion Tensor Imaging (DTI), it is almost certain that the discussed approaches must be subjected to revisions. The author's aim was rather to signal the need, particularly in the context of the current state of neuropsychological assessment capabilities, in the context of the increasing new opportunities not only to intra-brain connections imaging, but also its mathematical modeling (Sporns, 2012). The described cardiovascular system diseases may cause, particularly in advanced stages, changes in the subcortical areas of the brain, in some cases narrowed to the white matter. It is, therefore, a valuable

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area of clinical researches, which may contribute to better understanding of the white matter role in neuropsychological organization and regulation of cognitive processes.

Selected cardiovascular system diseases and malfunctions

Cardiovascular system dysfunctions are the main cause of death, lower quality of life and morbidity (Rosamond et al, 2008). Epidemiologically, in the year 2000 four millions of deaths were caused by cardiovascular reasons, and fatal strokes appeared in 505 300 men and 775 571 women in Europe (Graham et al., 2007). Besides genetic factor or congenial heart and vascular system anomalies, cardiovascular dysfunctions etiology is a combination of genetic and environmental / lifestyle conditions, mainly a fat diet, lack of sport activity, obesity, male sex, smoking, severe alcohol intake and other classical risk factors of cardiovascular diseases occurrence (Fowkes et al., 1992).

According to Framingham Heart Study (Cupples et al., 1987), cardiovascular system dysfunctions can be divided into four grups: 1) coronary heart diseases, 2) cerebrovascular diseases, 3) peripheral artery diseases and 4) heart failure. Besides heart injuries and malfunctions, there are also vascular dysfunctions, that play diverse role; on the one hand as a risk factor, and on the other as a comorbid disorder, those diseases are mainly hypertension and atherosclerosis (Kearney et al., 2005).

Cerebrovascular diseases are one of neurology and clinical, medical neuropsychology basic topics (Armstrong & Morrow, 2010). In turn, heart disorders, its damage as a result of coronary ischemia, are widely described in the cardiological and internal medicine. All of these diseases are a significant risk factor for the development of brain dysfunction and damage. The nature of these dysfunctions is strongly dependent on the clinical picture, the course and individual determinants of particular cardiovascular disease. Among them, one can distinguish those which accumulate slowly and are associated with the above-mentioned so-called risk factors i.e.: coronary artery disease, hypertension, atherosclerosis, carotid arterial stiffness, as well as a group of acute, rapidly emerging cardiovascular accidents such as myocardial infarction and cardiac arrest (Lim & Alexander, 2009). Additionally, there is a need to distinguish cardiac surgery cases, especially those with the use of an extracorporeal circulation.

In this paper there will be analyzed the conditions that are most common in the population, and are the most widespread risk factor changes for the brain dysfunctions.

Basic mechanisms of brain changes secondary to cardiovascular diseases and its cognitive consequences

As it was mentioned earlier, cardiovascular diseases (CVD) have various impact on brain, depending on whether the disease is slowly or suddenly rising. In the CVD spectrum, sudden cardiac dysfunction include cardiac arrest, for example, as a result of severe myocardial infarction (Waldstein et al., 2010). In cases of a longer than 4-5 minutes cardiac arrest, the most likely effect will be severe hypoxia / ischemia with irreversible brain damage, which often leads to coma. Besides the fact of global ischemia and hypoxia, there are however neural regions with special hypoxic damage vulnerability, that are most injured in the case of hypoxia resulting from cardiac arrest: small and medium-sized neurons of the striatum, the 3rd layer cortex neurons, thalamic neurons, and the Purkinjie cells of cerebellum. It also important to notice, that this severe state may be a direct cause of death.

The above described neural effects of cardiac arrest are typical of a rapid heart malfunction, that stops the blood circulation and leads to global hypoxia. As it was mentioned earlier, the most common cardiovascular diseases, like hypertension and atherosclerosis present different mechanism of brain injury. These mechanisms are complicated, with many comorbid modifying agents.

Hypertension is the basic, most common disease of the cardiovascular system. According to Kearney et al. (2005), the 972 million of adult people in the world suffered from hypertension, of whom 639 million in economically developed countries. It is anticipated that in 2025 there will be 1.5 billion of people with hypertension. This is a larger group of potential patients, than the groups of people with the central nervous system diseases (as a first disease) taken together.

According to Sierra and co-workers (2009), the main physiological vascular changes in the brain related to high blood pressure are: endothelial lesion due to mechanical stress, loss of vasodilatory capacity, increased vascular permeability, opened ionic channels, reduced lumen and hypertrophy of smooth vascular muscle, increased vascular resistance caused by smooth vascular muscle contraction, vascular stiffness, transudation of plasmatic products to arterial wall.

One of the factors leading to brain injury as a result of hypertension is progressive hypoxia and blood hypoperfusion. Hypoxia is caused by remodeling of blood pressure autoregulation. In normal brain, autoregulation enables to maintain the blood pressure at the stable level of 80/90 – 120/130 mmHg, and due to the hypertension, the autoregulation remodeling process starts and its parameters switches to a higher pressure measures (100/120 – 140/160 mmHg). In any period, when the pressure is normalized, the blood flow is insufficient for adapted regulation, which leads to hypoperfusion and hypoxia. The other injuring factors caused by hypertension are: excessive enlargement of the cerebral arteries, increasing blood flow and damage to the blood-brain barrier. It is also worth noticing, that prolonged hypertension trigger the characteristic changes in the microvasculature of the brain, the so called small-artery disease. Changes in small vessels lead to their almost complete closure or to formation of a microaneurysms. That is why, besides general white matter damage, the structures in which small arteries bring blood are susceptible to damage from hypertension (Monolio et al., 2003;Kadykov, Manvelov, Shahparonova, 2006).

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Atherosclerosis, highly correlated with hypertension, has also a complex etiology. The processes engaged in atherosclerosis progression are: the endothelial inflammation process, the high level of cholesterol, the endothelial damage and aggregation of cholesterol into the vessels wall, the oxidative stress, probably induced by smoking, and unknown viruses and bacteria – although the last ones are still hypothetical. The main process of atherosclerotic accumulation is creating of plaque in the vessel, but it is very important to point out, that those pathological vasculature changes additionally induce secondary pathological sequels. Those sequels are: calcification of atherosclerotic plaque which conducted the stiffening of the vessel, disturbance in the bloodstream flowing through the vessel in the form of vortices and reverse flow, damage to membranes and vessel walls leading to the formation of internal blood clots, vascular smooth muscle damage and failure. These changes lead to deformation of entire vessel groups (Ross, 1999; Naruszewicz, 2003; Waldstein et al., 2010).

Medical neuropsychology brought many proofs, that shortly described vascular changes leading to brain progressive injury are significantly correlated with cognitive dysfunctions and decline (Silverstein, 1959; Jodzio & Drumm, 2001; Manolio et al., 2003; Biechowska et al., 2007; Jodzio, 2008; Waldstein et al., 2010). Cardiovascular system malfunctions are also an important correlate of other medical conditions, that may cause brain injuries and secondary cognitive deficits, like: kidney diseases (Harciarek et al., 2011), or diabetes (Reijmer et al., 2013).

Cognitive consequences of cardiovascular burden, that do not have the severity of overt stroke / infarct, or vascular dementia, are called Vascular Cognitive Impairment (VCI) (Libon et al., 2009). According to Hachinski (Hachinski, 1994; Bowler & Hachinski, 1995; Devasenapathy & Hachinski, 2000) Vascular Cognitive Impairment term may be used to describe a broad continuum of cognition disturbances including mild and prodromal states of dementia correlated with vascular risk factors or vascular diseases. VCI might be treated as a set of rather mild but complex cognitive changes typical of patients with cardiovascular burden, but without primary, localized neuropsychological deficits caused by overt stroke, or overall cognitive collapse of the dementia type. Studies regarding the VCI neuropsychology describe often the following cognitive changes: impairment of executive control, visuoconstructive dysfunctions, slowing down of cognitive processing speed (Libon et al., 1998; Desmond, 2004; Libon et al., 2004; Price et al., 2005).

Cognitive consequences of hypertension and atherosclerosis, that should be included in the clinical picture of VCI, can be described with more details. Because those disease made changes in the brain vasculature, that was depicted earlier, some insights regarding its cognitive correlate can be established from the studies of carotid artery diseases It is important to notice, that cognitive sequels of hypertension are strictly connected with increased age of patients, taking (or not) the pharmacological treatment and its continuation in accordance with the medical recommendations.

One of the first reports on the presence of connection between carotid stenos is and cognitive decline was publication by Silverstein (1959), in which he remarked that in patients with severe carotid occlusion an "organic brain damage" may occur. However, detailed studies regarding associations between carotid vessel capacity in patients without a stroke and their neuropsychological status began with the development of medical neuropsychology as a distinct subdiscipline of neuroscience (Tarter et al., 2001). It is important to notice that there is: an easy, cheap, non-invasive, and available method of atherosclerosis diagnosis, mainly in the vessels important to brain functioning, which is the Ultrasonography (Doppler) of carotid arteries. This is a painless method of carotid atherosclerosis and stenosis high-precision assessment(Kaźmierski, 2011; Wojczal, 2011). There are already some results regarding relationship between atherosclerosis, especially in the areas of carotid vasculature and neuropsychological dysfunctions.

Empirical analysis carried out on a large research groups, containing people with asymptomatic carotid arteries disorders (without stroke or TIA) revealed a number of neuropsychological disturbances specifically related to carotid artery stenosis (CAS).
In the years 2004 – 2009, there were published at least three articles with detailed analysis of several hundred or several thousands of patients with asymptomatic CAS regarding their neuropsychological status. The results can be summarized as follows:

- there is a statistically significant reduction in overall cognitive functions in patients with substantial stenos of vessels supplying the brain, especially in the case of the left internal carotid stenosis,
- there is a significant, progressive cognitive decline in patients in whom, during one year stenosis persists or worsens, and it is not associated with a stroke or TIA,
- these results retain their statistical significance even when added to the quantitative analysis the other vascular risk factors, which is interpreted as an expression of the CAS specificity as an accurate indicator of vascular burden relevant to the deterioration of neuropsychological functions (Johnstone et al., 2004),
- subjects with asymptomatic CAS have obtained significantly lower scores in tests of: attention, psychomotor speed, memory and motor function, regardless of the MRI results, than those with identical demographic parameters, without pathological changes in the brain vasculature, who also had changes in the MRI (Mathiesen et al., 2004),
- the greater the degree of carotid stenosis ($\geq 25\%$ and $\geq 50\%$), the greater the severity of neuropsychological impairment of executive functions and nonverbal memory,
- the internal carotid artery atherosclerosis is a potentially stronger risk factor for the emergence of neuropsychological impairment than in the common carotid artery (Romero et al., 2009).

Besides general qualification of relations between cognitive functions and carotid artery atherosclerosis there were also conducted detailed qualitative analyses of cognitive decline in CAS. For example: Rao (2002) obtained the results indicating that neuropsychological correlates of CAS were: the reduction of parameters relating to executive functions: abstract thinking, cognitive plasticity, verbal fluency, as well as other symptoms of frontal dysfunction, such as impulsivity. In addition to this, the author also observed strong memory interference. Quite similar results obtained Kim et al, (2007), for example: in 14 of 16 patients cognitive impairment in more than one aspect of the processes such as attention, executive function, visual memory and verbal memory were identified. Executive dysfunction occurred in all subjects. Disturbances of other cognitive processes occurred in approximately 40 - 60% of the above mentioned patients.

White Matter Lesions: major neuroanatomical finding in patients with cardiovascular burden

There are several basic vascular mechanisms causing specific changes in white matter (WM). Part of them are described above. The white matter is especially vulnerable to damage secondary to CVD, because of the following factors:

- it is nourished mainly by small vessels which easily undergo dysfunctions and damage as a result of cardiovascular burden. It appears faster in life when compared with cortical vasculature changes.
- many white matter areas, particularly periventricular, are the terminal field of vascularization. These areas are located in the border scope of deep vascular branch and arteries originating from cortical branches of large arteries. Arteries supplying the WM does not produce anastomoses, and therefore deep border areas are more vulnerable to the progressive ischemia. This phenomena may be refered to the so-called "the last meadow infarct", which has similar origin (Pantoni & Garcia, 1995, 1997, Liao et al., 1996, Iskra, 2007, Sierra et al., 2009, Cohen, 2011).

Described pathological changes generate demyelination, axonal loss and substitution by glial cells. Brain regions of this characteristics manifest as the areas of low signal absorption coefficient in MRI, with elevated T2 and FLAIR (fluid-attenuated inversion recovery) sequences. WML affect mainly axons bundles in the areas around the ventricles, especially with a rostral and caudal distribution: anterior horn and secondly, posterior horns of the lateral ventricle. These regions may also be compared with anterior portion of the medial lenticulostriate vascular territory (Wen & Sachdev, 2004). Advanced WML are the risk factor for global brain tissue loss, and diffuse damages extending from the frontal lobe subcortical areas, occupying temporal lobe deep white mater, up to parietal and occipital white matter adjacent to cerebral ventricles walls (Walecki & Bulski, 2007). Detailed information regarding white matter

hyperintensities imaging with an application of MRI may be found in Yoshita et al publication (2005).

Cognitive sequels of white matter changes

Before considering the role of white matter in cognitive functioning, it is important to mark, that white matter changes can be a result not only of cardiovascular burden, but also the age itself. In the majority of studies regarding the described issues, patients aged over sixty, sometimes more than seventy are involved. The decreasing volume of white matter with increasing age, in people without neurological or cardiovascular diseases, has been confirmed in animal and human studies (Raz et al., 1997; Salat et al., 2004; Tapp et al., 2004; Decarli et al, 2005). There are some explanatory hypothesis of this phenomenon, for example Bartzokis and co-workers (2003; 2004) postulated that regional white matter decline is a form of white matter development reversed recapitulation. Myelin-producing oligodendrocytes operating during earlier stages of brain development are exceedingly vulnerable to injury, and it is so because of important differences in the axons they myelinate and decreases in their ability to repair. According to Peters (2002), age-associated white matter changes reflect probably myelin degeneration. It can be considered with the theoretical assumption, that brain during its life, especially in elderly people, present the progressive reduction of efficient neural connectivity (Albert, 1993).

Brickman et al (2006) publication can be considered as an excellent example of detailed, cross – sectional study the purpose of which was to examine relative white matter changes across the lifespan, and define the specific relations between: age, white matter and cognitive functioning, with application of MRI imaging and computer-administrated neuropsychological battery. The subjects in the study were 199 adults; the younger ones (21 – 30 years old), the middle aged (31 – 54) and the older ones (55 – 79), all without serious psychiatric, neurological, endocrine or cardiovascular diseases. Neuropsychological evaluation included the assessment of the following cognitive domains: choice reaction time, digit span (task for basic attention), verbal interference (similar to The Stroop Test), verbal memory and fluency, and switching of attention that was measured by the task similar to Trail Making Test.

The study results can be stressed as follows: the older subjects (55 – 79) had significantly less relative white matter than the middle and the younger groups. The young and the middle-aged groups were statistically similar in this aspect. The difference was greater in the frontal and temporal lobes. Participants from the oldest group had significantly reduced the frontal and temporal white matter compared to the other groups. All groups did not differ regarding the parietal and occipital lobes white matter. Significant correlations appeared between the age and neuropsychological test scores, except for the verbal fluency task. Neuropsychological tests performance significantly correlated with relative white matter especially in the right frontal lobe. The authors conducted a multivariate regression analysis to verify the obtained results. The analysis included:

the age, the right and left frontal, the right and left temporal lobe white matter. Only the age and the frontal lobe white matter were a significant predictor of neuropsychological tasks with a particular reference to executive and memory functions. In general, the results of this study indicate that the reduction in white matter volume, occurring within the frontal areas may also be found in healthy persons, and are associated with age. Thus, changes in the white matter, especially in the frontal lobes does not have to result from vascular burden, especially in people aged over 55.

Analyzing the publications regarding white matter and cognitive functions relations, one may find, that most of them concern the occurrence of white matter dysfunctions in older people, patients with MCI or with various cardiovascular burden, while there are only few works devoted to detailed research on relationship between specific cognitive functions and different white matter areas. In other words, the issue of specific functional specialization, if it exist, of the white matter is still an open area for empirical exploration. One of those rather rare publications is a metaanalysis made by Debette and Markus (2010) whose goal was systematic review of white matter hyperintencities[1] (WMH) clinical importance, with the application of magnetic resonance imaging and cognitive functions assessment. They have taken 53 publications under account that met the established inclusion criteria. Apart from the white matter changes participation in the risk factor group for the emergence of various dementia types, they found that periventricular white matter hyperintensities (without deep matter WMH) are significantly, and almost exclusively connected with cognitive processing speed reduction and executive function decline. Secondary to above mentioned processes was memory, conceptualization ability and visouopractical skills.

The next article contains more detailed information about the white matter changes impact on cognitive functions. Marquine et al (2010) purpose was to answer the question about the differences between anterior and posterior white matter hyperintensities cognitive correlates. 110 participants, aged between 60 and 83 years, and with at least a high school education took part in their study. MRI imaging was made at baseline and after approximately 2 years. The authors applied many cognitive tests and trials, that were divided by them into five cognitive domains: complex processing speed, working memory, executive functions, memory / language processes and visuo-constructional skills. The main results may be stressed as follows: changes in complex cognitive speed were associated with anterior WMH progression, while changes in viso-constructional skills with posterior WMH. Summing up their study, they conclude, that decline in cognitive speed is independently correlated with anterior and overall WMH progression. Those results are similar to those obtained by Longstreth et al (1996), van der Henvel et al, 2006 and van Dijk et al., 2008.

A part of Rotterdam Study conducted by de Groot and others (2000) was also focused on the possible white matter impact on selected neuropsychological variables.1077 nondemented subjects, aged 60 – 90 took part in the study. The administrated methods of cognitive assessment contained: Letter-Digit task, similar to one of the WAIS subtest, verbal fluency, verbal memory and global cognitive evaluation (MMSE). The authors divided white matter changes into subcortical and periventricular types. The results support the mentioned thesis of age significant impact on white matter damage, both subcortical and periventricular. There was also general association between subcortical and periventricular WMH and overall cognitive performance level, but, the periventricular index proved to be stronger marker for changes in cognitive functioning. An important factor here is that white matter lesions cause the significant decline in cognitive speed, especially the lateral bundle of periventricular WM. There was no association between subcortical WMH and cognitive speed. In general de Groot et al, believe, that mainly periventricular WMH stronger than subcortical, correlated with cognitive impairment. This occurs because when short subcortical connections are disrupted, they disconnect adjacent cortical areas. Schmidt et al (1993) stated that only complex mental processes are affected by periventricular, and to a lesser extent, subcortical, white matter changes, leaving the single functions unaltered. De Groot et al interpret their results in the following way: "The performance on the multiple neuropsychological tests (…) depends on the connections between many cortical areas, not necessary adjacent, thus depends mainly on the long association tracts" (de Groot et al., 2000, p. 150).

The above mentioned suppositions should be enriched by the results obtained by Cook and his colleagues (2002). They focused on the connectivity parameters in researches regarding the relation between brain damage and cognitive decline. Applied methodology was a combination of volumetric MRI measurements, neuropsychological assessment and coherence of electrophysiological brain activity in nondemented elderly subjects. The coherence parameters were indexed by quantitative EEG (Leuchter et al., 1994) and additional software that measure the co-occurring brain activity on the same frequency, and compare the activity from above two areas relevant to the main connections between cortical and subcortical structures. This method permits testing the hypothesis, that changes in deep brain structures primarily induce the disconnection phenomenon. The conclusions of Cook et al study are: white matter damages affected the cognitive functioning, and especially the performance of tests relying mainly on complex cognitive processing speed. Increased periventricular hyperintensities volumes were highly associated with the coherence index in prerolandic and postrolandic regions. In general, electrophysiological coherence showed associations with many other cognitive functions, however in different manner and strength. Therefore, the authors conducted the path analysis. The

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[1] The term „white matter hyperintensities" refers to neuroimaging studies using the MRI, and this kind of researches was the article's basis. One should mention that in studies using the CT, pathological white matter changes will be imaged as hypotensive.

result was that altered connectivity does mediate the effects of white matter disease on cognition and Trail Making Test part B performance, and additionally, cognitive plasticity and working memory form an indicator of complex cognitive speed processing. This process is probably the most important correlate of generalized disconnection syndrome resulting from diffuse white matter damage.

Executive, visuospatial and attentional deficits appears not only in white matter damage. In recent years several author attempted to determine the specific neuropsychological and neurological disorders profile, which would be typical of the white matter damage. Differences between cognitive dysfunction in the case of cortical and WM lesions have been repeatedly discussed on the example of cortical and subcortical dementias, which pointed to differences in language (often impaired in cortical dementias, and probably not in subcortical), memory - with dominant disorder of encoding in cortical type and recovery information from memory in subcortical, as well as the occurrence of procedural memory disorders in subcortical gray variant, which probably not occurring in cortical dementias (Cummings& Benson, 1984, Filley, 2001). Jose M Lafosse and his colleagues (2007) highlighting the diversity of subcortical dementias attempted to answer the question whether there are differences in disturbed and preserved cognitive processes between subcortical gray matter (eg, basal ganglia, thalamus) damages and white matter lesions. Choosing a clinical groups characterized primarily by damage to subcortical gray matter (Huntington's disease) and WM (Multiple Sclerosis) and the wide range of cognitive measures determined that: 1) there are many similarities between the two groups regarding attention and memory - both groups achieved better results in verbal recognition subtest than reproduction, 2) there were differences between groups regarding learning skills and procedural memory in terms of sequence learning consisting in the fact that these functions were significantly more impaired in the group with subcortical gray matter damage than WM lesions. Filley with coworkers (1988, 1989), based on the comparison of the WM damage cognitive effects and subcortical gray dysfunction indicates that the typical image of neuropsychological disorders occurring in WM lesions consist of: deficits in sustained attention, with relative sparing of attention focusing and switching, disorders of memory retrieval with normal procedural learning; according to Markovitsch (1995) the uncinate fasciculus is responsible for memory retrieval because of necessity to connect working memory (anterior brain parts) with episodic and semantic memory (posterior parts, mainly temporal lobes), memory disturbances can also be referenced directly to the alveus demyelination, which are expected phenomena, given the fact that this structure is adjacent to the lateral ventricle wall (Haines, 2002), cognitive slowing and spared language function with exception in case of arcuate fasciculus damage.

Cognitive processing speed decrease as a white matter dysfunction marker

Analyzing the previous empirical material it is easy to see that slowing of information processing speed is the most common disorder observed in the white matter dysfunctions, particularly in periventricular areas. It should be noted that the authors use the term complex cognitive processing speed, with reference to dynamic aspect of performance, while measuring complex cognitive tasks such as working memory, as is the case with Trail Making Test Part B. It is not a simple process analogous to the response time, but the realization speed of complex tasks involving multiple cognitive processes, with different disseminated neuronal distribution.

Before the further analysis of relations between the white matter and cognitive speed, it is important to notice, that mental slowdown was one of the core features of the subcortical dementia concept introduced mainly by Albert with coworkers (1974) and Cummings (1990). Although there were previously published work, which also concerned the specificity of subcortical brain dysfunction - for example by von Stockert (1932). According to Filley (2001), the concept of bradyphrenia, meaning precisely mental processes slowdown, have been introduced already in 1922 by Neville. This concept has become one of the focal points of the subcortical dementia concept, which somehow re-occurred in the 70-ies of XX century (Albert, 2005). However, subcortical dementia characterized by mentioned authors was mainly a result of subcortical grey matter damage – for example basal ganglia, subthalamic nucleus, and cortex in progressive supranuclear palsy, neostriatum, substantia nigra, and later cerebral cortex and hippocampus in Huntington disease, pars compacta of the substantia nigra in Parkinson disease and other rather rare degenerative conditions affecting mainly basal ganglia, thalamus and various areas of the diencephalon and brain stem (Cummings, 1990). Demyelinating diseases and vascular / ischemic white matter damages were also mentioned among brain damages causing subcortical dementias, therefore it raises the question, whether the white matter is specifically connected with complex cognitive speed.

Currently, the use of devices such as Diffusion Tensor Imaging (DTI), allowing accurate white matter structures observing, encourages to conduct research on complex cognitive processing speed determinants. One such study was published by Turken et al. (2008) and it deserves a fuller discussion because the researchers combined the methodology of modern neuroimaging and lesion studies.

In the first phase of the study they engaged 39 young healthy subjects (mean age: 22.4 ± 3) whose task was The Digit-Symbol subtest from WAIS-III. During the performance, the DTI images were taken, including fractional anisotropy (FA) and voxel based morphometry analysis (VBM) to show the detailed fibers picture. Cognitive processing speed correlated with different white matter areas of which the hypothetical were divided into five clusters: 1. left parietal areas with corona radiata (superior) and superior longitudinal fasciculus, 2. right parietal areas

with similar structures as in the 1st cluster, 3. left middle frontal gyrus with superior frontal-occipital fasciculus, anterior thalamic radiation and extreme capsule, 4. left temporal lobe including: inferior longitudinal fasciculus and inferior occipito-frontal fasciculus and uncinate, 5. right temporal lobe with inferior longitudinal fasciculus, inferior occipito-frontal fasciculus and optic radiation. The researchers found no cortical brain structure that correlate with complex cognitive speed. Conducted variance analysis which included variables such as age and sex, revealed that structures most associated with cognitive processing speed were: left parietal and right temporal areas with inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, superior longitudinal fasciculus and posterior section of corona radiata and secondary: fronto-striatal projections. All mentioned here white matter structures are long association fibers, that connect distant brain areas.

In the second study phase, 72 patients (61.1 ± 11.6 years old) with left hemisphere stroke (single cerebrovascular accident) took part. They were tested approximately 12 month post-onset. The cognitive task was the same as before. The average Digit-Symbol performance of patients did not reach the level expected fromthe normal population (4.5 versus previous group: 11.92). The authors applied DTI voxel-based lesion-symptom mapping. The analysis revealed an association between cognitive processing speed reduction and lesions in parietal white matter, especially with superior longitudinal fasciculus and corona radiata. The other white matter regions was a pyramidal tract, external capsule and anterior and posterior parts of internal capsule. The voxel based morphometry showed that significant association region was left parietal white matter, mainly in the area consistent with superior longitudinal fasciculus trajectory. It is worth noticing, however, that unequivocal localization was not fully possible in the letter group because the there appeared lesions that go beyond the designated brain regions.

Before discussing described results, one should not overlook that in the newest publication by Duering et al (2013), considering neural correlates of cognitive processing speed in 235 subjects with pure vascular disease (caused by CADASIL syndrome), the authors obtain results that differ from those previously depicted. Duering and colleagues applied Trail Making Test part A and B, and the block design test, which proved to be valid methods of cognitive speed assessment (Duering et al., 2011) and MRI imaging, with distinction of two damages types: lacunar lesions and white matter hyperintensities. Additionally, the authors used a sophisticated statistical analysis, which allowed them to generate multivariate image of damaged brain structures associated with slowing of information processing. Those structures were: parahippocampal white matter and corticospinal tract hyperintensities and lacunar changes in the areas of cingulum and anterior thalamic radiation. All those structures made a functional network with forceps minor.

Comparison of brain structures that emerged from the Turken et al study, and those described above, shows some significant differences. Although there are some similarities regarding temporal white matter structures, the appearance of cingulum in Duering study is new. In explaining these differences one should take into account, that the main information processing speed assessing method in the Duering et al study, was the Trail Making Test. Its performance depends not only on the information processing speed, but also – and especially part B –on the cognitive flexibility and an efficient working memory. These are the dimensions belonging to the executive functions. Dinnen et al, 2008 and Sasson et al, 2012 studies may help in explaining the effect of cingulum damage in the cognitive processing speed. According to these authors, cingulum is a major correlate of processing speed in executive task performance. Nevertheless, confronting various studies, it is rather clear, that complex cognitive processing speed is based on white mater associative and projection structures.

Repeatedly confirmed relationships of cognitive processing speed and various white matter areas, including the specific neural fibers and bundles require further explanation. Marsel Mesulam (1998, 2000) proposition is that synchronization and integration of many co-occurring cognitive activities are supported by brain networks operating on the basis of long-range information transmissions across distributed neural structures and connections. Neural signal speed transmission and accuracy of cognitive processing are related to axons thickness and the degree of myelination (Tolhurst & Levis, 1992, Gutierrez et al, 1995). In addition, according to other authors, the efficiency of cooperation between various brain areas and the neural signal transduction process depends also on temporal precision (Engel et al, 2001) and the ability of long association tracts to resist signal degradation (Catani & ffytche, 2005). Complex cognitive processing speed require all those white matter features, especially the capacity factor of white matter, that supplies fast, full and thorough information permeability.

Interpretations and conclusions: from disconnection to neural networks and information processing dynamics

Researches with application of Diffusion Tensor and Magnetic Resonance Imaging are not the first attempt in neuropsychology, to understand the role of white matter in cognitive functions regulation. It was not only Wernicke with his conduct aphasia model, but also other well known neuroscientists who do not agreed with strict cortical locanizationism like: Lichtheim, Dejerine, von Monacow, Meynert, Fleshing, Papez, English neurologist Sherrington and Scottish psychologist Bain, and polish neurophysiologist Konorski (1967), who could be considered as an early precursors of the neural network theory and processes of the brain self-organization (Catani & Thiebaut de Schotten, 2012). There is rather no doubt, that Norman Geschwind's theoretical proposition were cannectionism major fundamentals.

In his two publications, printed in *Brain* (1965 a, 1956 b), Geschwind presented the neo-associationist theory mainly devoted to disconnection syndromes.

These syndromes were the result of damage to specific brain structures: first, the white matter pathways, second, to associative cortex. Norman Geschwind's proposal was widely received by neuroscientists, as an important breakthrough in the neurosciences, which was dominated by the localizationism views. It is inspiring to many researchers who have developed it, and are still developing it in terms of modern neural network theory. Analyzing Geschwind's disconnection syndromes, one will find that they relate to disconnected localized cortical areas, and thus, these syndromes are like the next installment of thinking about the brain as a collection of separated cortical and subcortical areas, the failure of which evoke specific, clearly defined syndromes. The diagnosis of disconnection syndromes takes on a very similar form to the recognition of deficits resulting from localized cortical lesions, i.e., it is also a zero-one: there is or not a disconnection. It is difficult to determine, for example, following the footsteps of Geschwind's thinking, that in some patients there is a slight form of pure alexia.

Connectionist thinking developed into the network approach, which emphasized the dynamic aspect of the brain functioning. Besides, neuroscientists abandoned the narrowly localized approach to the brain systems, to extended territories composed of many subregions with more complex cognitive activity (Boatman, 2004, Damasio et al, 2004).

Localized brain areas became nodes forming the epicenters of specialized networks, as it is depicted in Mesulam's large scale networks for cognition and behavior (1990, 2000).

In terms of Mesulam approach, in the brain one can distinguish not only individual cortical areas of specific morphology, but the structural and functional networks, responsible for complex cognitive functions (Mesulam, 1999, 2000). Analyzing Mesulam's proposal, it is worth pointing out that in this approach, brain damage will disturb these functions as a result of separation - not individual fields of the cerebral cortex, but the cortical-subcortical systems that are more diffuse than disconnected areas in Geschwind's model.

Even more advanced theoretical model of brain dysfunction syndrome is The Hodotopic Model by Catani and ffytche (2005). As a progressive proposal to be considered by them, is the hypothesis that cortical areas themselves can beunderstood according to network approach. In this model, the surface brain areas are called functional territories, which are specialized as structures connected by local, short U - shaped fibers. Those territories are connected via long associative tracts of white matter. The second relatively new approach is that disorders of connectivity can also produce hyperconnectivity, as it is observed in epilepsy or schizophrenia (Liang et al., 2006, Schmitt et al., 2011). Hodotopical mechanism (which refers to path or road topology) is mainly a pathway dysfunction regardless of disconnection, hypoconnection, hyperconnection or mixed conditions. Thus, hodotopically-related dysfunctions are disconnections combined with local hyperconnectivity and distant hypoconnectivity (or vice versa) (Catani and Thiebant de Schotten, 2012).

All connectionist models having its origin in the nineteenth century, including the latest, and consider the role of white matter in linking the cortical and subcortical gray matter structures and enabling their mutual interactions. Thus, cognitive dysfunction arising with the WM damage, in this sense, have their origin in the gray matter dysfunctions. Beside the connectionism, similar understanding is the assumption that subcortical dysfunction lead to secondary hypofunctionality of the cerebral cortex, as a result of its lack of the bottom - up stimulation (Jodzio, 2011). The Reed and coworkers researches (2004) positively verified the hypothesis of a subcortical ischemic lesions significant impact on cortical activity measured by PET. The authors divided the subcortical damages to lacunes located mainly in the thalamus and basal ganglia and diffuse white matter changes. They also took into account to measure the effectiveness of verbal memory, executive functions and global cognitive index, whose composed of indicators of learning, verbal fluency and attention. The results can be stressed as follows: subcortical lacunes were significantly associated with regional cerebral glucose metabolic rates of the dorsolateral frontal cortex. Prefrontal hypometabolism and executive dysfunctions were significantly associated with anterior cortical atrophy. White matter lesions were connected with global reduction in cortical metabolism rate, and global cognitive index but not with frontal cortex nor executive functions as it was noted regarding subcortical gray matter structures. There are also other studies showing that white matter changes (but not subcortical gray matter) are not significant predictor of cortical hypometabolism (DeCarli et al., 1996, Sabri et al., 1999, Tohgi et al., 1998), or that they affect the generalized and non-specific metabolism in the entire brain (Takahasi et al., 2000). Above results, although shown only in certain aspect, suggests, that the cognitive functions, which may also be disturbed after cortical damage (executive, memory and visual-spatial) undergo pathological changes due to disconnection of grey matter structures and / or secondary cortical hypometabolism being the result of previously described mechanisms.

All discussed data tend to ask the question: does the white matter only connects the grey matter structures that generate and process information or is involved in the coordination of these processes? Does the cognitive disturbances that appear in the diseases accompanied by white matter changes are only the result of secondary cortex and the grey matter structures disorders?

In order to approach the answers to these questions it is worth to look closer at the white matter damages at a more basic level. Studies of Ihara and colleagues (2010) show that the vascular cognitive impairment and vascular dementia are particularly characterized by myelin loss, more than Alzheimer disease and dementia with Lewy bodies. White mater is prone to ischemic damage in a form of a myelin shrinking. Felts et al (1997) and later Sinha et al (2006) stated that myelin damage does not always mean total interruption of signal transmission in axons – what is assumed a priori in disconnection models. If the neural tissue is not broken, demyelinated axon conducts potentials but in significantly changed temporal organization. Even partially demyelinated axons transmit the signals with reduced

velocity, and their refractory period of transmission is about 34 times prolonged that the value obtained from normal myelinated axon (Felts et al., 1997). Those data indicate that ischemic white matted damage leads to slowdown and dysregulation in the information transmission process on the basic physiological level. What is also important, studies carried on by the Bertzokis team (2010) have shown that interference in the transmission of signals at the cellular level are significantly associated with a slowing at the behavioral level.

These findings suggest that dysfunction of the white matter, consisting of ischemic myelin injury may lead to cognitive decline not only by their effect on the gray matter, as described earlier, but also by changes in the nerve signal transmission. According to O'Sullivan and coworkers "slow performance places greater demands on the retention of information in working memory and possibly other memory systems" (O'Sullivan et al., 2004, pp. 1145). In cases of significant cognitive slowing, subject executing the cognitive task must maintain in mind a given volume of information, much longer than the normal processing rate. This means that the performance of tasks involving many different mental processes (eg, attention, memory, phonological loop, imagination, etc.) will be ineffective at cognitive slowing. In schizophrenia (if it appears in cardiovascular disorders is still an open question) cognitive processing speed was a specific factor, which contributed to the differences between patients with schizophrenia and healthy controls regarding such a cognitive domains as: executive functions, attention, verbal / visual memory, and working memory (Ojeda et al., 2012). It means, that decrease in processing speed weakens the results of tests measuring the basic cognitive functions. Retention of information may also be the basis of capacity to maintain mental set – function similar to sustain attention. Results obtained by Lamar et al (2002) indicate that patients with ischemic vascular dementia (IVD) comparing to non-demented healthy control and participants with Alzheimer disease, committed more errors regarding the capacity to maintain task demand over a specific period of time.

In classical neural network theories (Shallice, 1988; Plaut, 1996) networks have at least two fundamental features: parallel and distributed processing. White matter damage, which reduce network integrity (Filley, 2010, Burgmans et al., 2011), may cause volume of information processing and its completeness diminution. This can be explained with regard to networks characteristics of distributed processing. Therefore, one must ask a question: what happens to the temporal dimension of network information processing – i.e. simultaneity of processing, in cases of networks damages? In the light of described data the hypothesis can be, that complex processing speed due to diminution of edges in networks and dynamic irregularity of processing induces the necessity of changes in the organization of network connections, perhaps in the form of searching for the conductivity "by-pass" for the damaged regions and its connections. If it appear, the processing speed in the networks must also change.

Martin L. Albert in his paper summarizing the personal history of research on subcortical dementias concludes: "Perhaps the real contribution, in years to come, of the introduction of 'subcortical dementia' to the study of dementias will turn out to have been its emphasis on timing (rate of information processing) and dynamic (turning on, turning off, maintain flow, switching) aspects of the contributions of subcortical structures to emotion, personality and cognition". (Alber, 2005, pp. 224). Highlighting interferences in information *p r o c e s s i n g*, its speed, regularity, uniformity, maintaining mental set and regular information flow (Snyder & Cappelleri, 2001), integrating multiple processes, with which one find in Albert's statement fit well to the study of ischemic white matter damages and their cognitive consequences. Reduction of processing speed, a specific neuropsychological marker of white matter lesions should not be treated as an isolated phenomenon mentioned alongside other disorders, but – it can be determined with high probability – an important factor in appearance of executive, attentional and memory disorders. It is worth notice, that there is a fully developed theory of brain / mind functions that focuses entirely on neural and psychic processes (Brown & Tomaszewski, 2012; Kropotov & Mueller 2012).

The main method of assessing white matter structural changes are MRI and DTI. Given the specificity of WM functions, it appears that additional research - including those posed above verification thesis - in the future, could be carried out using methods imaging the information processing (and not the location of the cognitive modules). Some of EEG methods, ranging from event related potentials allow to study the dynamic dimension of the cognitive flow, their results enable trace these processes in the millisecond scale. Still rare works on the evoked potentials (amplitude and latency) show that patients diagnosed with hypertension are characterized by prolonged latency - not the amplitude – of the N2 and P3 components. In addition, in hypertensive group the diastolic blood pressure significantly correlated in with N2 wave latency associated by the authors of the study with the sensory information processing (Tandon & Joon, 1997).

Given the presented discussion regarding potentially different determinants of neuropsychological disorders resulting from white matter damage there appear questions that may determine the possible future areas of research :

1. What is the principle that enables the coexistence of different mechanisms leading to the creation of neuropsychological disorders in patients with vascular white matter lesions – whether the different mechanisms described above are associated with qualitatively different profiles of cognitive dysfunction in the indicated group?

2. As previously mentioned, slowing of information processing have been reported in patients with various forms of subcortical dementia. On the other hand, a recent study using different methods and methodologies indicate that it corresponds to the white matter damages,

including the cellular level for the dynamic aspect of the process information. This raises a question about the possible diversity of the symptoms on the dynamics of information processing in patients with damage to the white matter and subcortical gray matter structures.

Attempts to answer these questions - although it is not a closed list - can contribute to a deeper understanding of the nature of neuropsychological deficits in patients with damage to the white matter .

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