EFFECTS OF CAROTID ENDARTERECTOMY ON THE NEURAL BASIS OF WORKING MEMORY AND ATTENTION

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TIIVISTELMÄ

Kaulavaltimon endarterektomia (CEA) on kirurginen toimenpide, jolla ennaltaehkäistään aivoinfarkteja hoitamalla kaulavaltimoahtaumaa. Toimenpide voi parantaa aivojen verenkiertoa ja sitä kautta sillä saattaa olla vaikutuksia myös kognitiivisiin toimintoihin. Magnetoenkefalografia (MEG) mahdollistaa tiedon saamisen siitä, kuinka toimenpide voi vaikuttaa kognitiivisen toiminnan taustalla olevaan aivojen sähköiseen toimintaan. Aikaisemman tutkimuksen tulokset eivät ole yhteneväisiä siitä, miten toimenpide voi vaikuttaa kognitiiviseen toimintaan. Tarkkaavuuden ja työmuistin neuraalisia mekanismeja ei ole aiemmin tarkasteltu MEG:n avulla CEA:aan liittyen. Tutkimuksessamme tarkastelemme, vaikuttaako tämä toimenpide työmuistin ja tarkkaavuuden neuraaliseen perustaan MEG:lla mitattuna. Analysoimme tapahtumasidonnaisia herätevasteita (ERF) kolmelta eri mittauskerralta leikkaushoidon jälkeen (n=5). Työmme on eksploratiivinen ja se tarjoaa suuntaviivoja sille, mitä tekijöitä tulevassa tutkimuksessa pitää ottaa huomioon. Tutkimuksemme tuloksien perusteella ei voida osoittaa, että toimenpiteellä olisi selkeää vaikutusta tarkkaavuuden tai työmuistin neuraaliseen perustaan. Löysimme viitteitä siihen, että leikkaushoito vaikuttaa tarkkaavuuteen liittyvään aivojen sähköiseen toimintaan, mutta näiden muutoksien merkitykset ovat epäselviä. Tutkimuksemme johtopäätös on, että tulevissa tutkimuksissa on perusteltua käyttää toiminnallisen aivokuvantamisen menetelmiä yhdessä kognitiivisen suoriutumisen arvioinnin kanssa, jotta leikkaushoidon mahdolliset vaikutukset kognitioon ymmärrettäisiin paremmin. Myös operoidun kaulavaltimon puolen mahdollinen vaikutus on syytä huomioida.

AVAINSANAT: kaulavaltimon endarterektomia, CEA, kognitiiviset toiminnot, tarkkaavuus, työmuisti, magnetoenkefalografia, tapahtumasidonnainen herätevaste, ERF

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ABSTRACT

Carotid endarterectomy (CEA) is a surgical method done to prevent strokes by treating stenosis. The procedure can improve cerebral circulation and thus might also affect cognitive functioning. Magnetoencephalography (MEG) provides a method to gain insight on how the operation affects the electrical mechanisms of the brain related to cognition. Previous research is inconclusive regarding the effects of CEA on cognitive functioning. The neural mechanisms of attention and working memory related to CEA have not previously been studied with MEG. In this study we examine whether carotid endarterectomy affects the neural basis of working memory and attention with MEG. We analyze event-related fields (ERFs) from three different measurement sessions after the operation (n=5). Our study is exploratory and provides insight into what aspects should be considered in future studies. The results of our study do not indicate that the operation has clear effects on the neural correlates of attention and working memory. We did find indications that the operation affects the electrical activity of the brain related to attention, but the meaning of these changes is unclear. The conclusion of our study is that future research should utilize functional brain imaging methods together with cognitive performance evaluation to better understand the effects on cognition. The side of the operated carotid should also be taken into account.

KEYWORDS: carotid endarterectomy, CEA, cognitive functions, attention, working memory, magnetoencephalography, event-related field, ERF, evoked response

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1. INTRODUCTION

Carotid endarterectomy (CEA) is a widely used surgical procedure to prevent subsequent complications arising from carotid stenosis, which is a major risk factor for ischemic stroke (Flaherty et al., 2013). Stroke remains as a major global burden - in 2013 it was the second leading cause of death (Feigin, Norrving & Mensah, 2017) and it has been estimated that by the year 2025, about 1.5 million individuals suffer a stroke per year in Europe alone (Béjot, Bailly, Durier & Giroud, 2016). Transient ischemic attacks (TIAs) and major ischemic strokes are also related to various neurocognitive and physical impairments, such as memory dysfunction (Al-Qazzaz, Ali, Ahmad, Islam & Mohamad, 2014), post-stroke depression (Robinson & Jorge, 2016) and communication problems (Brady, Kelly, Godwin, Enderby & Campbell, 2016). In addition to preventing strokes, CEA might improve cognitive functions that may have impaired due to reduction of cerebral blood flow caused by the stenosis (Wang et al., 2015). Yet, the decision to perform CEA is primarily based on the likelihood of preventing a stroke while the possible benefits for cognitive functioning are not taken into consideration.

Even though there are studies examining the effects of CEA on cognitive functioning with behavioral tests (e.g., Ghogawala et al., 2013; Heyer, Mergeche & Connolly, 2014; Qu et al., 2015), most of the studies done show inconsistency between their results. To better shed light on this issue, it is important to study the neural basis of cognitive functioning. Currently, few studies have examined how CEA affects the electrical functioning of the brain with different means of electroencephalography (Czerny et al., 2010; Shi et al., 2016; Valenti et al., 2015; Vriens, Wieneke, Huffelen, Visser & Eikelboom, 2000). The aim of our study is to contribute to this question and give new information with magnetoencephalography whether CEA affects fundamental cognitive processes; the neural basis of working memory and attention.

1.1 Carotid endarterectomy and cognition

Carotid endarterectomy (CEA) has been shown to be an effective treatment for both symptomatic (Rothwell et al., 2003; Orrapin & Rerkasem, 2017) and asymptomatic (Aboyans et al., 2018; Goldstein et al., 2006) patients. The operations are mainly carried out to prevent subsequent complications, such as ischemic strokes which could be fatal. Because the operation affects cerebral perfusion, it can be hypothesized that CEA also has an effect on cognitive functioning (Ghogawala et al., 2013; Wang et al., 2015). Despite the research done, there is still a vast uncertainty whether cognitive functions are affected by the operation (Paraskevas, Lazaridis, Andrews, Veith & Giannoukas, 2014; Rango et al., 2008). Since working memory and attention are the cognitive processes that can be assumed to be the most vulnerable to deficits when cerebral blood flow is impaired, it can be hypothesized that these functions are affected the most by CEA.

Cerebral circulation is disrupted by carotid stenosis (Fang et al., 2016) and carotid artery atherosclerosis with over 50% stenosis is a major cause of ischemic strokes (Petty et al., 1999). There are three ways in which atherosclerosis causes strokes: rupturation of plaques can cause thrombus to format, the artery can occlude or dislodged parts from plaques can lodge carotid artery branches (Prasad, 2015). CEA achieves plaque passivation by physically removing harmful plaque (Safian, 2017). The severity of stenosis is based on the degree of the stenosis, indicated by how much the artery is blocked with percentages. It has been widely studied that carotid artery stenosis impairs cognitive functioning (Johnston et al., 2004; Lal et al., 2017; Wang, Mei & Zhang, 2016). In addition, the CEA itself might impair cognitive functioning by hypoperfusion caused by clamping or by microembolic ischemia during the operation (Lal et al., 2011). On the other hand, CEA could improve cognitive skills by increasing cerebral perfusion (Wang et al., 2015). Plessers, Herzeele, Vermassen & Vingerhoets (2014) have estimated CEAs effects on cognition postoperatively. They conclude that there is impairment in neurocognitive functioning of approximately in 10-15% of patients and in 10% of the cases there is improvement (Plessers et al., 2014).

Previous studies on whether CEA has effects on the cognitive functioning measured by pre- and postoperative neuropsychological tests are inconclusive. Some of these studies present a decline or no changes in cognition (Bossema, Brand, Moll, Ackerstaff & Van Doornen, 2005; Pearson, Maddern & Fitridge, 2003), while others show improvement in cognitive functions (Lal et al., 2011; Wang et al., 2015). It has been stated that CEA has no per se effect on postoperative cognitive changes (De Rango et al., 2008).

The differing results express the fact that currently there is no consensus about the cognitive outcomes of CEA. One of the major reasons for the inconsistencies are methodological differences, which include the usage of control groups, psychometric tests, heterogeneity of the patients and the timing of cognitive evaluations (Lunn, Crawley, Harrison, Brown & Newman, 1999; Plessers et al., 2014). Regarding the assessment of cognitive skills before and after CEA, the results are often affected by learning effects, sample sizes and by the side of carotid stenosis (Lunn et al., 1999; de Rango et al., 2008).

1.2 Working memory and attention in the context of cerebral blood flow

The two fundamental cognitive processes - attention and working memory are tightly intertwined together (Knudsen, 2007) in that they are difficult to distinguish from each other, both theoretically and behaviorally. However, they are very easily disturbed by even the most minor cerebrovascular events. The basis for the vulnerability of these cognitive domains lies in the system of cerebral circulation and the neural basis of attention and working memory. Consequently, vascular mechanisms have been shown to play a crucial role in cognitive impairment (Chen et al., 2017; Gorelick et al., 2011).

Usually the carotid stenosis begins at the common carotid artery (CCA), extending to the internal carotid artery (ICA). ICAs along with vertebral arteries supply blood to the whole brain, consequently ICA stenosis decreases global perfusion of the brain and it relates to the degree of the stenosis (Fang et al., 2016). ICAs further branch to anterior cerebral arteries (ACA) and middle cerebral arteries (MCA), which form the two major cerebral arteries. Combined together they contribute to form the anterior circulation of the brain. MCAs account for relatively 80% of the blood flow into hemispheres and the ramifications of these arteries supply subcortical nuclei and dorsolateral frontal, temporal and parietal cortices, as well as other areas (Nagata et al., 2016). Consequently, reduced blood flow due to stenosis can impair the functioning of these areas.

The vertebral arteries originating from subclavian arteries supply the posterior circulation of the brain. Vertebral arteries further join together and form the basilar artery, which enables blood flow from internal carotids to join into the circle of Willis. Posterior cerebral arteries also originate from this formation and they supply deep structures within the posterior forebrain in addition to supplying anterior circulation. Importantly, this formation combines all the major arteries that supply blood into the brain. It also has a major function in compensating the blood flow reduction in carotid arteries, making it one of the most crucial structures in the case of carotid stenosis (Hartkamp, Van Der Grond, Van Everdingen, Hillen & Mali, 1999). The main collateral blood flow routes within the circle of Willis are shown to be the anterior communicating artery (AcoA) and posterior communicating arteries (PcoA) (Hoksbergen, Fülesdi, Legemate & Csiba, 2000).

Despite this collateral circulation, carotid stenosis causes disruption in neurovascular mechanisms and it can provoke cognitive impairment (Buratti et al., 2014; Tao et al., 2018; Wang, Mei & Zhang, 2016). The decrease in the cerebral blood flow affects especially attention, memory and executive functions (Alosco et al., 2013; Román, Erkinjuntti, Wallin, Pantoni & Chui, 2002). Attention is the ability to select, maintain and manipulate relevant information, which all are crucial for daily tasks as well as for more demanding cognitive tasks. According to Ronald A. Cohen’s (2014) neural model of attention, attention is an interplay between a network of subcortical structures (thalamus, striatum and limbic nuclei) and the structures of the cortex (temporal lobes and the posterior association areas), where the reticular activating system (RAS) plays an important role. It originates from the brainstem and travels through the thalamus to the cortex. Together these networks and structures contribute to maintaining different attentional processes (Cohen, 2014). The neural pathways of attention include wide regions of the brain, leaving it vulnerable to deficits when cerebral circulation is compromised, as in carotid stenosis. Subcortical structures such as basal ganglia and thalamus are at especially high risk when blood flow is compromised, because the blood flow maintained into subcortical areas is provided by long arteries and narrow arterioles (Moody, Bell & Challa, 1990).

Similarly to attention, the functioning of working memory (WM) is also crucial for completing everyday tasks, making it one of the first functions amongst attention to show impairment when cerebral circulation is altered. It refers to the capability of temporarily maintaining task-related information in an active state so that relevant sensory information can be held and connected with past experiences, knowledge and skills. Consequently, it facilitates the manipulation of information from different sources for fulfilling ongoing tasks. The concept of WM is a topic of ongoing debate in neuroscience and there are plenty of theories of WM’s nature. In theoretical literature, attention is described as a gatekeeper for working memory – it selects and gates what material to let into further processing of working memory (Awh, Vogel & Oh, 2006). WM tasks during brain imaging have been shown to consistently activate a widespread fronto-parietal network, which can be considered as a core network for WM functioning. (Rottschy et al., 2012).

1.3 Functional neuroimaging of attention and working memory

Altered cerebrovascular hemodynamics, such as possible post-CEA revascularization, can project to the brain's electrical activity via neurons altered electrical function. This alteration in the brain's electrical functioning can be measured directly by brain imaging methods such as magnetoencephalography (MEG) (Ohtomo et al., 2009) and electroencephalography (EEG). The basis of both methods lies in the activity of groups of parallelly oriented pyramidal neurons. While EEG measures the electrical voltage, MEG measures the magnetic fields of postsynaptic potentials. Both methods have been used to examine the neural basis of working memory and attention. In addition to these methods, the brain’s electrical functioning can be measured indirectly with functional magnetic resonance imaging (fMRI), which is based on regional paramagnetic deoxyhemoglobin changes measured with blood-oxygen level-dependent (BOLD) activity (Ogawa, Lee, Kay & Tank, 1990). When comparing these methods, fMRI has poorer temporal resolution than MEG or EEG, but fMRI has significantly better spatial resolution (Glover, 2011).

The most frequently used paradigm in brain imaging studies to examine the neural correlates of working memory is the n-back task. This highly demanding task recruits key functions of the working memory, such as monitoring, updating and manipulating information (Owen, McMillan, Laird & Bullmore, 2005). The core idea of the task is to report if the current stimulus is similar to previously presented stimuli, usually in the span of one, two or three (Rac-Lubashevsky & Kessler, 2019). However, n-back performance may not fully correlate with the performance in the Digit Span working memory test, which is commonly used in neuropsychological assessments (Miller, Price, Okun, Montijo & Bowers, 2009). Therefore, it is unclear whether the n-back is a valid measure of pure working memory.

Functional magnetic resonance imaging studies have shown that all variants of n-back tasks, regardless of the target feature, activate dorsolateral prefrontal and parietal regions and prefrontal activity increases linearly when working memory load is increasing (Jacola et al., 2014; Moisala, 2017). The task is sensitive to frontally mediated cognitive functions (Miller et al., 2009) and these regions are considered as neural substrates for working memory processes (Jacola et al., 2014). Owen et al. (2005) examined modified n-back tasks with different input modalities in their meta-analysis. They conclude that there are task and content related nuances in brain activation seen in either subregional level or hemispheric lateralization. Tasks requiring verbal monitoring of stimuli such as letters and numbers increase activation in the left ventrolateral prefrontal cortex, an area that is also important for inner speech. Conversely, tasks requiring non-verbal location monitoring are related to increased activation in the right dorsolateral prefrontal, lateral premotor and posterior parietal cortex, which are formulated as a spatial attention network (Owen et al., 2005). Furthermore, it has been found that there is a connection between the working memory load on the n-back task and the activation of the dorsolateral and inferior frontal regions of the prefrontal cortex; increased activation of these areas is associated with poorer performance in healthy participants when load in task is increasing. (Miller et al., 2009).

Working memory is inherently intertwined with attention (Knudsen, 2007), so working memory tasks such as n-back tasks rely on both functions. Attentional processes are modulated by two segregated systems: top-down selection of attention and stimulus- driven (bottom-up) attention (Corbetta & Shulman, 2002). Aforementioned n-back task can be assumed to reflect top-down attentional functions, because it requires conscious control of attention. These top-down processes are dependent on the functioning of the posterior parietal cortex and prefrontal cortex (Katsuki & Constantinidis, 2014). In addition, the prefrontal cortex seems to be involved in changing the context during top-down processes as well as in short-term memory functions (Bauch & Itti, 2011).

To conclude, working memory is highly distributed and linked across sensory, parietal, temporal and prefrontal areas. Each area creates a different kind of representation about encoded stimuli (Christophel et al., 2017). Posterior regions process perceptual information, frontal regions process the rehearsal of the stimuli and sustain attention to the task and the parietal cortex has been related to executive aspects of working memory and selective attention control (Eriksson, Vogel, Lansner, Bergström & Nyberg, 2015).

While fMRI studies have significantly contributed to mapping out the brain areas required for working memory tasks such as the n-back task, event-related potentials (ERPs) from EEG-studies and event-related fields (ERFs) from MEG-studies have been used to study the brain's electrical functioning more directly. ERPs are small voltages which reflect the electrical functioning of the brain in response to various events, such as to sensory stimuli or cognitive events (Luck, 2014) and ERFs can be considered to be their magnetic equivalent. Still, they are not completely comparable to each other since MEG and EEG differ slightly (Baillet, 2017). MEG has excellent spatial and temporal resolution due to the magnetic permittivity of different compartments remaining stable, whereas in EEG the differences in the electrical conductivity of various compartments affect the signal (Baillet, 2017).

There are also methodological differences in how working memory is studied between EEG and MEG. In MEG studies the focus is mainly on neural oscillations, which is rhythmic neuronal activity. For example, it has been studied that theta and gamma rhythms are linked to memory functions, whereas attentional processes are linked to alpha and gamma rhythms (Ward, 2003). Furthermore, it has been found that medial frontal theta waves are related to n-back task (Brookes et al., 2011). Also, in EEG studies the alpha frequency band is correlated with tasks that involve attention and working memory (Eriksson et al., 2015).

In ERP components research the focus is in the timing, strength and polarity of peak amplitudes related to information processing. Early components, such as P200 and N200 waves, reflect sensory processing of stimulus (Luck, 2014) and the later components, such as the P300 wave, reflects higher cognitive processing of stimulus (Polich, 2007). All aforementioned components can be linked to working memory and attention. P3b is an attention and memory related sub-component seen at 250-500 ms post-stimulus, stemming from temporal-parietal activity and varying with the modality of stimulus (Polich, 2007). P200 at 150-300 ms after stimulus (Luck, 2014) originating from parieto-occipital areas (Freunberger, Klimesch, Doppelmayr & Höller, 2007) has also been associated with working memory and it may have a connection with allocation of attention (Lijffijt et al., 2009). N200 at 200-300 ms (Luck, 2014) is originating from temporo-occipital areas in case of visual stimulus, and it is thought to reflect visual attention (Folstein & Van Petten, 2008). Stronger parietal P3b and P200 amplitudes together with smaller N200 amplitudes in the same area are related to better performance in n-back tasks (Morrison, Kamal & Taler, 2019). There seems to be differences in ERP components between healthy individuals and persons suffering from deficits. For example, individuals who have mild cognitive impairment (MCI) elicit smaller P300 amplitudes and the delayed latencies of the P200 and N200 components during the n-back task (Zunini et al., 2016). In addition to these early and later components, there are also components that can be seen much later than the components mentioned above, such as the N700 component. This component originates from occipito-temporal areas in response to visual stimuli at 500-1200 ms, representing stimulus post-processing (Bender, Behringer, Freitag, Resch & Weisbrod, 2010). Thus, various components can be used to investigate cognitive functions.

There are only a few studies examining the brain's electrical activity before and after the CEA. To our knowledge none of these employs the n- back- paradigm as a way to study the neural responses elicited with the task. Czerny et al. (2010) conducted an EEG- study to examine how CEA affects the P300 auditory evoked potentials with a 5-year follow-up time in 25 patients with symptomatic and high-grade ICA stenosis (over 80%). They used the odd-ball paradigm and found that after CEA the P300 potentials were statistically significantly shortened and the effect sustained after 5 year, which were interpreted to indicate improvement of cognitive functioning (Czerny et al., 2010). Shi et al. (2016) also examined the P300 event-related potentials, before and 3 months after carotid endarterectomy. Similarly, they found a reduction in the P300 score, which was interpreted as indicating improvement of cognition (Shi et al., 2016). Another study by Vriens et al. (2000) used quantitative EEG (qEEG) to examine alpha rhythm 3 months after CEA. They found statistically significant improvements in mean and peak frequency of the alpha band. The mean and peak frequency increase was seen in the posterior areas of the brain, and the peak frequency increase was also seen in temporal and central areas of the brain. These were assumed to be related to the improvement in cerebral circulation after CEA (Vriens et al., 2000). A second study using qEEG by Valenti et al. (2015) focused on the findings preoperatively and 5 months after CEA. They found out that mean EEG dominant frequency increased in patients with severe bilateral stenosis. Here the mean frequency was weighted by the relative power of beta, delta, alpha and beta bands in addition by the power of each frequency band. Changes in qEEG were assumed to be related to improvements in psychometric tests (TMT-A, SDT) (Valenti et al., 2015).

These EEG studies illustrate that CEA has effects on the electrical functioning of the brain and it is reasonable to study the effects of CEA with brain imaging. Research on the effect of CEA on the electrical functioning of the brain, especially working memory performance, is scarce and MEG studies are non-existing. Furthermore, the studies do not provide direct information about the neural correlates of working memory, of which n-back is a commonly used paradigm. Combining MEG imaging with the n-back paradigm provides a way to more directly study the neural correlates of working memory with better spatial resolution than with EEG.

1.4 The aim of this study

This thesis focuses on studying whether CEA affects the electrical activity of the brain related to working memory and attention using MEG. The research questions are:

1.Does CEA affect the brain's electrical functioning underlying attention and working memory?
    a) Is there a change in the cognitively demanding 2-back working memory task?
    b) Is there a change in the easier control task?
2. Does the change seen in the electrical activity last for one year?

Because the 2-back task is highly demanding and engages various key functions of the working memory (Owen et al., 2005) and attention can be seen to facilitate the functioning of WM (Awh et al., 2006), we assume that a change seen in event-related fields (ERFs) to only this task indicates that carotid endarterectomy affects the brain functions underlying specifically working memory. If a change in the ERFs related to the control task alone or to both of the tasks can be seen, we assume that CEA affects more general regions of the brain underlying attentional processes. This is based on the notion that our control task is similar to a 0-back task, in which sustained attention is essential but it does not have demands for working memory (Miller et al., 2009) while the working memory task engages both attentional and working memory functions. Since there are few studies examining the effects of CEA after one year or more of the operation (Plessers et al., 2014), we do not have an assumption to whether the effects of CEA are long-lasting.

2. METHODS

This study is a part of a larger CEAMEG project (Kukkonen et al., 2019), which has been reinforced with two additional participants, whose data are included in our study. In the project the participants underwent three MRI, neuropsychological and MEG sessions: before (preoperation), 3 months and 1 year after CEA. During the MEG-recordings participants engaged in a 2-back working memory task and a control task. Cognitive functioning was evaluated by a set of neuropsychological assessments, including visuoconstructional, verbal, attention and memory tests. In this study, we only analyze the data from MEG recordings, but we refer to the results of neuropsychological tests in the discussion.

2.1 Participants

The participants (n=6) of this study were recruited and operated in the Central Finland Health Care District (KSSHP) during the years 2017-2018. The MEG recordings took place in the years 2017-2019. One participant was dropped out of the study due to complications from the surgery and is not included in our data. Consequently, our final sample size consisted of five participants. Four (80%) of them were men and one (20%) woman. They all had symptomatic carotid stenosis; three (60%) of the subjects had suffered a TIA (transient ischemic attack), one (20%) had suffered an AFX (amaurosis fugax; a temporary loss of vision of one or both eyes due the lack of blood flow) and one (20%) had suffered a stroke. The ages of the subjects varied between 69-77 years (mean = 73; standard deviation = 3). The degrees of the stenoses were between 55-90% (mean = 72%; standard deviation = 17.3%). Three (60%) of the participants were operated on the left side and two (40%) on the right side. In addition, possible cognitive impairment was screened with Mini-Mental State Examination (MMSE), where the cut point indicating normal cognitive functioning is often set at 24 (Creavin et al., 2016). Four (80%) of the participants scored over 25 points in the MMSE test across all three sessions, while one (20%) of the participant scored lower than 25 points (20 and 24 points) in MMSE over two different sessions.

When the decision to perform carotid endarterectomy was made together with a vascular surgeon and the patient, the patient was informed about the study and asked to participate in the study. Written consent was given if the patient was willing to participate. Exclusion criteria included difficult aftermath following a stroke defined as a modified Rankin Scale score of over 3 (Swieten, Koudstaal, Visser, Schouten & Gijn, 1988), severe dementia, metal objects inside of a body (which could prevent the usage of MEG), significant psychiatric diseases, problems with intoxicants, drugs that affect the functioning of central nervous system, cancer in active stage and frequent symptoms from cerebrovascular diseases.

2.2 Magnetoencephalography recordings

The MEG sessions were done in an interdisciplinary brain research center in the university of Jyväskylä with Elekta Neuromag TRIUX (Megin Oy, Helsinki, Finland) using a whole-head system consisting of 306 channels. The measurement sessions were carried out before the operation (preoperation, M0), three months (M3) and one year (M12) after. The equipment records the strength of magnetic fields at 102 different locations, each location having two planar gradiometers oriented orthogonally and one magnetometer. We only used the recordings from gradiometers in our study. Participants underwent MEG recordings in a magnetically shielded room after being instructed about the procedure and after the removal of any clothes or metal objects that could distort the recordings. They were also asked to avoid moving their heads if possible. To localize the participant's head, five head position indicator (HPI) coils were attached to each participant's scalp. The localization was continuous since the coils were in an activated state. The participants' anatomical landmarks (preauricular points and nasion) and the general shape of the head was digitized with Polhemus Isotrak (Polhemus, Colchester, VT, United States). Eye movements were monitored by electro-oculogram (EOG) electrodes as follows: one above the right eye, one below the left eye and one ground electrode on the collarbone. Electrocardiogram (ECG) was monitored by having electrodes above collarbones (at the midway of each collarbone).

The stimuli during MEG recordings were controlled using a presentation program (Neurobehavioral Systems Inc., San Francisco, CA, USA). The participant was seated in the chair with their head inside the MEG helmet while the different tasks were displayed on a white screen in front of the subjects which was located one meter away. Their dominant hand was placed on the response pad on the table. Resting state was also measured for four minutes with eyes open at the start of the experiment and for eight minutes with eyes closed at the end of the experiment.

2.3 Stimuli and task

Two separate task conditions were used. The 2-back task consisted of two blocks, which both lasted for four minutes. There was a brief pause between the blocks. During the blocks, participants were shown numbers ranging from one to seven, one by one, in the middle of the screen. The same number was not repeated twice in a row. Each number was displayed for 300 milliseconds. The interstimulus interval (ISI) from the offset of one number to the onset of the next number varied between 2450-2950 ms. During the ISI, a fixation cross was presented in the middle of the screen. The participant was instructed to continuously sum up the last two numbers that were shown. Participants had to then decide with a press of a button (yes/no) if the number in a green frame was the combined sum from the two previous numbers. The possibility for the green frame to show up after at least two numbers had been shown was approximately 20% (the total percentage for the green frame to show up during the whole task was approximately 14%). 50% of the time the green frame displayed the correct sums and 50% of the time it displayed incorrect sums. An illustration of the 2-back task is shown in Figure 1. The participants got to practice the task before the actual measurements took place to ensure that participants had understood the instructions given.

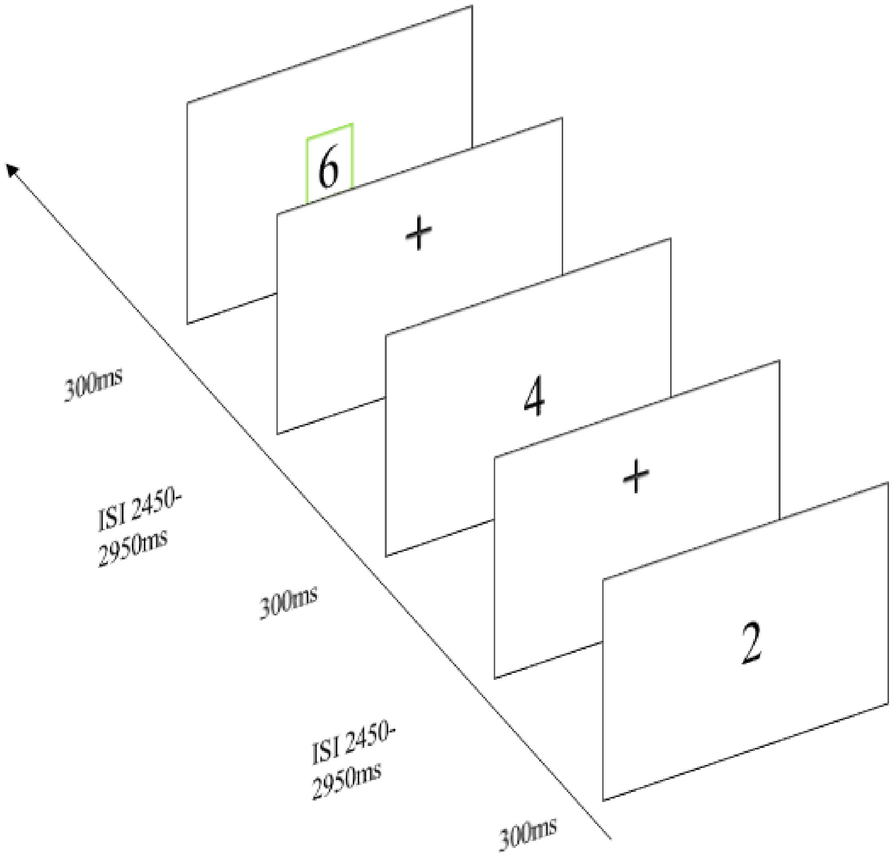

FIGURE 1. Illustration of the experimental procedure during the 2-back task.

The control task consisted similarly of two blocks, which lasted for four minutes each and there was a brief pause between the blocks. During the blocks, the participant was shown numbers one by one ranging between one and nine. The stimulus was presented for 300 ms, preceding an interstimulus-interval of 2450-2950 ms. The participant was instructed to press a button when the number one was displayed on the screen. In this task the number was not framed. A fixation cross was present in the middle of the screen during the ISI. Again, the participants got to practice the task beforehand to ensure they had understood instructions.

2.4 Magnetoencephalography data preprocessing and analysis

The MEG data was collected at a sampling rate of 1 kHz during the recording with a low-pass filter set at 330 Hz and a high-pass filter at 0,01 Hz. Bad channels were excluded from the data using Xscan 2.2 software (Elekta Neuromag). The data was preprocessed with MaxFilter 2.2 (Elekta Neuromag). Temporally Extended Signal Space Separation (tSSS) (Taulu, Simola, Nenonen & Parkkonen, 2014) with a subspace correlation threshold of 0.95 was applied to remove interference. Head movements were compensated with HPI coils. The data was also downsampled by a factor of 3. After preprocessing the data was imported into Meggie for further processing. Physiological artefacts, eye blinks and heartbeats (EOG and ECG) were removed using signal-space projection (SSP).

Epochs time-locked to task onset were generated for a time window of -200 ms before stimuli to 1200 ms after stimuli. The measurements from the individual magnetometers and gradiometers for each epoch were split into nine pools corresponding to different brain areas. The locations of gradiometers in their respective brain areas can be seen in Figure 2. These areas are approximates, because no anatomical data of the participants' brain areas was used when grouping the pools to different locations. The pools were averaged in each location to obtain event-related fields (ERFs) from these nine locations. They correspond approximately to the left and right sides of the occipital, temporal, parietal and frontal areas as well as the vertex. These were stored in an Excel (Microsoft Corp.) spreadsheet, which was further analyzed and visualized with Python. Some visualizations were also done with Excel. Every epoch where the participants were shown a green frame during the 2-back task or had to press the button for yes/no answers was excluded from the data analysis, to avoid the contamination of electrical activity related to decision-making and activity caused by hand movements.

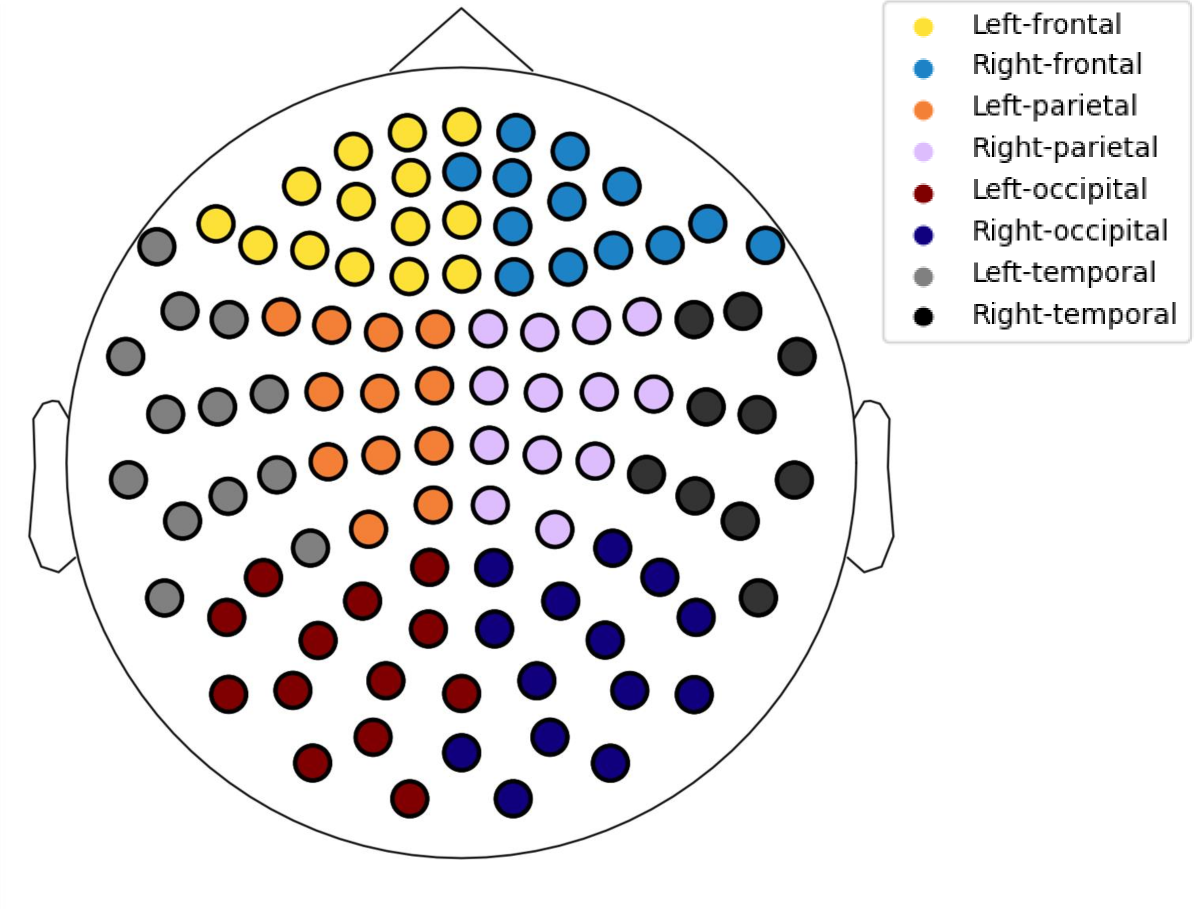

FIGURE 2. Positions of the gradiometers and the defined brain areas for occipital, parietal, temporal and frontal areas.

Previous research has shown that the different time windows of ERFs represent different phases of the cognitive processes. Earlier time windows reflect basic sensory information processing while later time windows reflect higher cognitive processing, such as evaluating stimulus and memory functions (Banaschewski & Brandeis, 2007). Based on this knowledge, we divided epochs into three different time windows: early (50-250 ms), middle (250-600 ms) and late (600-1000 ms) time windows. The values of each participant's ERFs were extracted and averaged to each of these time windows. Consequently, we obtained a single value from each of the time windows representing the mean value of ERF in each brain area for both of the tasks separately. This was done separately for every brain area and time window from both of the tasks by each single session. Statistical analyses were done for these mean values based on knowledge about their role in the cognitive process.

The ERFs mean and standard deviation between subjects for statistically significant results can be found in Appendix A. They are displayed for each time point and brain area for both of the tasks (2-back, control), with the time windows highlighted. The data was plotted using Seaborn library.

2.5 Statistical analysis

Quantitative analyses were conducted with repeated measures analysis of variance in IBM SPSS Statistics software, version 26. The analyses were constrained to areas representing left and right sides of the occipital, parietal and frontal areas. We compared the means of ERFs elicited by 2-back and control tasks separately for the selected combination of brain areas and time windows across sessions. This was done by having the task (2-back, control) and the time of the measurement session (preoperation, 3 months, 1 year) as within-subject factors. In the cases where sphericity assumption was violated, the results were interpreted using Greenhouse-Geisser correction.

For occipital areas we chose ERFs from the time windows of 50-250 ms, 250-600 ms and 600-1000 ms since the early ERFs reflect the visual sensory processing carried out by occipital areas. For parietal areas we chose the ERFs from the time windows of 250-600 ms and 600-1000 ms and for frontal areas we chose ERFs from the time window of 600-1000 ms, because these areas are crucial for working memory functions and later ERFs reflect higher perceptual processing. The data from the temporal and vertex areas was noisy and from a theoretical basis not central to our analysis, hence we excluded it. In addition, boxplots were made to represent the distribution of the mean amplitudes (Appendix B). The boxplots illustrate the mean amplitudes of the ERFs in the chosen brain areas of interest and time windows for both of the tasks separately. Boxplots were plotted with Seaborn library.

Our data had a total of 23 (6.4%) extreme outliers and 32 (8.9%) outliers including all the three sessions. An observation was defined to be an extreme outlier, when its value was three times the length of interquartile range above the third quartile or below the first quartile. Similarly, value was defined to be a mild outlier if it was one and a half the length of interquartile range above the third quartile or below the first quartile. Interpretation of these outliers was done by boxplots.

We brought extreme outliers close to the normal distribution’s tail to prevent type II error - the acception of the false null hypothesis. This was done by giving new values to extreme outliers. The new values were the nearest integer to the distribution’s tail. The order of the participants' values was retained in this procedure. Per sessions the extreme outliers were distributed the following way: in the first measurement (preoperation) there were five, in the second measurement (three months) there were six and in the third measurement (1 year) there were 12. The control task had 15 while the 2-back had eight extreme outliers including all the sessions. Mild outliers were not brought close to the normal distribution's tail because of our small sample, as boxplot could interpret actual values too sensitively as being outliers. Mild outliers were distributed across three sessions as following: 10 in the first measurement (preoperation), 12 in the second measurement (three months) and 10 in the third measurement (one year). The control task had 15 mild outliers while the 2-back had 17 including all the measurements. The distribution of the extreme and mild outliers per participant, brain area and time window across all the three measurements can be seen in Table 1.

TABLE 1. Number of extreme and mild outliers together per participant in different brain areas and in specific time windows of event-related potentials across all the three measurements.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Left-occipital					
50-250 ms	2		5		
250-600 ms	6		2		
600-1000 ms			3		
Right-occipital					
50-250 ms	1	1	6		
250-600 ms	1				
600-1000 ms	6	1		2	
Left-parietal					
250-600 ms		3			
600-1000 ms	1				
Right-parietal					
250-600 ms	3				1
600-1000 ms	2	1			1
Left-frontal					
600-1000 ms	2			1	
Right-frontal					
600-1000 ms	2	2			

After giving the extreme outliers new values, we examined the normality with the values of skewness, kurtosis and their z-values. In addition, we used Shapiro-Wilk's test of normality ($p < .05$) and inspected the visual characteristics of normal QQ-plots. The z-values that were in the range of -2.0 – 2.0 were considered to be normally distributed. By these methods, our data was mainly normally distributed. However, the late ERF (600-1000 ms) of the control task one year after carotid endarterectomy in the right side of the parietal area was not normally distributed when examined with Shapiro-Wilk's test of normality ($p < .05$).

When interpreting the results, we emphasize the role of effect sizes for the differences between means measured with Cohen's d, because our sample size is small. We consider Cohen's d threshold values to be .20 for small, .50 for medium and .80 for large effect sizes (Cohen, 1988). To avoid type I error, the elimination of true null hypothesis, we only report and interpret large effect sizes ($d \geq .80$).

3. RESULTS

First, we inspected the data visually to gain information about the patterns of activity in the ERFs in response to the tasks. Then we inspected the main effect of session (preoperation, 3 months, 1 year) in each task (2-back, control) separately to find out whether the ERFs elicited by them differed across the sessions in each of the chosen areas and time windows. Repeated analysis of variance was conducted using the time of measurement (preoperation, 3 months, 1 year) as a within- subjects factor. Then we studied the interaction between tasks and sessions to see whether the change in ERFs across time of measurements is different between the 2-back and the control task in each brain area and time window. Repeated measures analysis of variance was conducted using the time of measurement (preoperation, 3 months, 1 year) and task (2-back, control) as a within-subject factors. We did not find any statistically significant interaction effects of time of measurement and the type of the task, but we still analyze the main effects of sessions, because of the explorative nature of our study and because of the small sample size. In addition, we were interested to see if the possible change would last for one year.

3.1 General overview of activation pattern

The expected activation pattern evoked by stimulus is visualized in Figure 3, which shows the pre-operative mean amplitudes and standard deviations for each time point in the right-occipital, right-parietal and right-frontal areas for the 2-back task. Standard deviation is depicted with colored spread around the fixed line, while the different colors represent each time window. In the right side of the occipital area the activity is seen as a clear peak in the early time windows, while for the right sides of the parietal and frontal areas the activity is more sustained in later time windows.

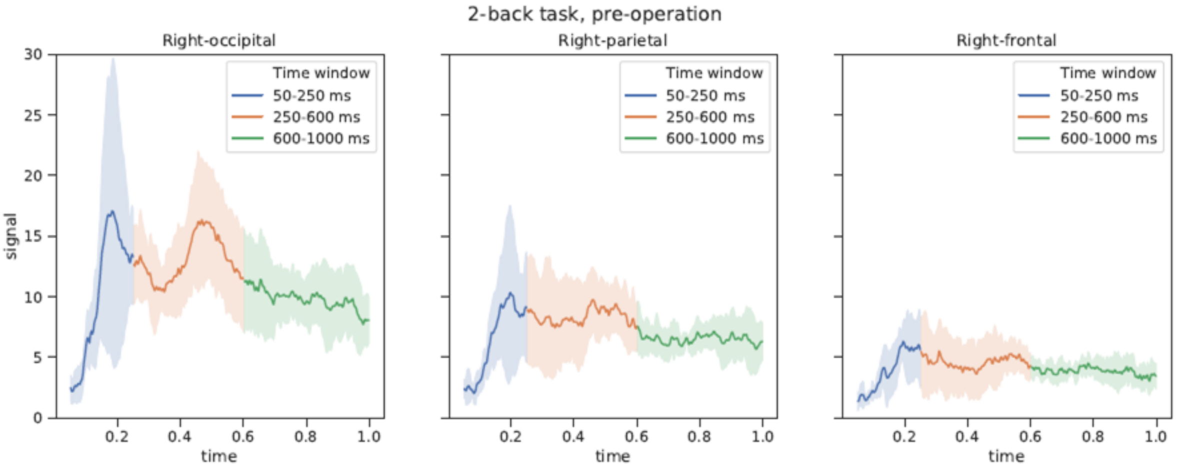

FIGURE 3. Illustration of the expected activation pattern of ERFs in the right side of the occipital, parietal and frontal areas during the 2-back task in the first session (preoperation).

These time windows seem to show a transient activity in the early time window in the right side of the occipital area (50-250 ms), which is typical when a visual stimulus evokes sensory activity in the brain and more activity during the middle window (250-600 ms). This activity decreases over time and is accompanied by emphasized activity in the parietal areas during the middle (250-600 ms) time window. There is more sustained activation during the late window (600-1000 ms) in the right side of the frontal area. This corresponds to our choice of time windows and the general structure of ERFs in our data. In general, there is a strong ERF amplitude in the early time window in the occipital areas during both tasks.

The visual overview also indicates that the variance between participants in the mean amplitudes of ERFs is large. The variance is considerably large in the third session when compared with the first (preoperation) and second (3 months) sessions in most of the brain areas. As Figure 4 indicates, the variance in frontal areas between individuals is especially large in the 1-year session, which is likely to be due to stronger noise in one or several individuals. Also, the variance between individuals is large in the parietal areas one year after the operation as Figure 4 depicts. The variance between individuals on the activity of the occipital area is quite large, however the variance seems to be stable between the sessions. Probably the variance is due to stronger noise in one or several individuals. Visualization of the raw data showed that the variance is likely from one subject.

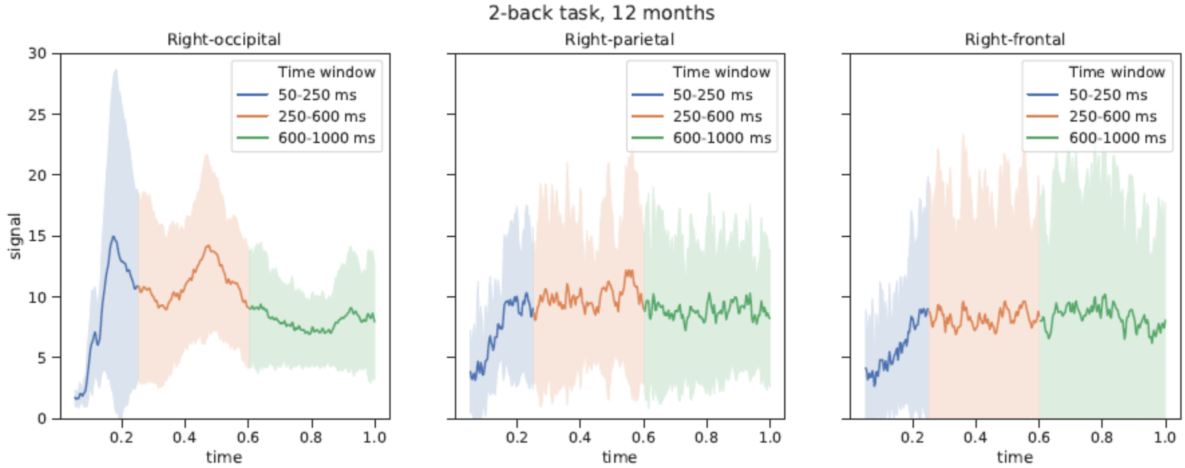

FIGURE 4. The mean amplitudes of the 2-back task in the right sides of the occipital, parietal and frontal areas at 1 year after the operation.

3.2 Occipital area

When examining the effects of measurement time (preoperation, 3 months, 1 year) for ERF's in each task separately, no statistically significant results were found. However, when examining the results with Cohen's d for the 2-back task, a large effect size is seen in the right side of occipital area during the early ERF (50-250 ms) when comparing the first and second session (d = .92). Between these sessions the means of ERFs decrease (Appendix C, Table 2). For the control task, the effect size were large in the late ERF (600-1000m) in the right side of the occipital area when comparing the first (preoperation) and second (3 months) (d = 1.77) and first and third (1 year) (d = .82) sessions. Here the mean values of the ERFs increase between the sessions (Appendix C, Table 3).

When looking at the interactions and main effects, no statistically significant interactions were found (Appendix C, Table 4). Instead, we found a statistically significant main effect on the type of the task in the right side of occipital area during both the middle ERF (250-600 ms) (F(1,4) = 22.318, p < .01, η_p^2 = .848) and during the late ERF (F(1,4) = 11.980, p < .05, η_p^2 = .750). The means of ERFs elicited by control task were systematically lower across all the sessions than the ERFs elicited by the 2-back task. In addition, we found a statistically significant main effect on the type of the task in the middle ERF of the left side of the occipital area (F(1,4) = 17.335, p < .05, η_p^2 = .813). Here the ERFs' means were again systematically lower for the control task compared with the 2-back task across all the sessions.

3.3 Parietal area

No statistically significant results were found when looking at the effects of measurement time (preoperation, 3 months, 1 year) for each of the tasks individually. When looking at the effect size measured by Cohen's d, it is large for the control task in the middle ERF (250-600 ms) in the left side of the parietal area when comparing the first and third session (d = .90). The mean ERFs increased between the first session to the third session (Appendix C, Table 3). No statistically significant interactions or main effects were found (Appendix C, Table 4).

3.4 Frontal area

One statistically significant result was found when examining the effects of measurement time (preoperation, 3 months, 1 year) for each of the tasks separately. The late ERF (600-1000 ms) in the left side of the frontal area elicited by control task differed statistically significantly across the measurements ($F(2,8) = 5.385$, $p < .05$, $\eta_p^2 = .574$). However, multiple comparisons with Bonferroni corrections were not statistically significant (preoperation vs. 3 months, p = 1.00; preoperation vs. 12 months, p = .251; 3 months vs. 12 months, p = .125). When multiple comparisons were done with LSD corrections (practically no correction was used) we found out that the second session differed statistically significantly from the third session (p = .042). The means of the ERFs increased between the second and the third session (Appendix C, Table 3). In addition, the value of Cohen's d is large when this variable set is compared with the first and second session (d = 1.47). The mean of the ERF increases between these sessions. No statistically significant interactions or main effects were found (Appendix C, Table 4).

4. DISCUSSION

Our study investigated the effects of carotid endarterectomy on the neural correlates of working memory and attention via improved cerebral blood flow. We examined event-related fields (ERFs) from brain areas and time windows generally assumed to be related to the functioning of working memory and attention, namely the early, middle and late ERFs from the occipital area, middle and late ERFs from the parietal area and late ERFs from the frontal area. The working memory related brain activity was induced by the 2-back task paradigm. Our control task was similar to the 0-back condition, which does not require working memory, but relies on sustained attention (Miller et al., 2009).

The first research question was whether the electrical activity of the brain underlying the working memory and attention was affected by CEA. We hypothesized that a possible change in the ERFs related only to cognitively demanding the 2-back task would indicate that the operation affected brain areas that are in control of working memory functions. On the other hand, we assumed that a change in the ERFs regarding the easier control task alone or both the control and the 2-back task would indicate that the operation affects brain regions that are responsible for general attentional processes.

Our study found changes in the ERFs regarding both 2-back and control tasks after CEA. The mean values of ERFs increased amongst the control task in the right side of the occipital area in the late ERF (600-1000 ms) when comparing the first (preoperation) and second (3 months) sessions, in addition to when comparing the first and third (1 year) sessions. The mean of the ERFs elicited by the control task in the left side of the parietal area during middle ERF (250-600 ms) increased between the first and third session. Likewise, the mean value of the late ERFs (600-1000 ms) regarding control task in the left side of the frontal area increased between the first and third sessions. Finally, there was only one change in the ERFs related to the 2-back task; the early (50-250 ms) mean value of the right side occipital areas decreased between the first and third sessions.

The expected visual information processing pattern of ERFs consisted of emphasized activation in the occipital area during the early time window followed by the activation of the parietal and frontal areas during later time windows. This pattern was found in our study. However, when we inspected the change in the activation patterns of ERFs in their respected time windows, we found unexpected results, namely a differential change between the left and right sides of the brain during the control task. This could be explained by the fact that the control task requires processing of symbols, which is a left-lateralized function.

4.1 Changes in the neural correlates of attention

Our results show that there were much more changes in the ERFs related to the control task than in the 2-back task after the CEA. This indicates that the operation affected more the neural correlates of the control task that requires sustained attentional functions over working memory functions (Miller et al., 2009). Because we observed more changes in the control task, we address these results first.

The change in the ERFs in the late (600-1000 ms) time window of the left frontal and parietal areas during the control task can be related to top-down control of attention, since the posterior parietal and prefrontal cortices are related to attentional control (Katsuki & Constantinidis, 2014). This is in line with studies that have shown that later event-related potentials reflect higher cognitive processing (Banaschewski & Brandeis, 2007).

However, the increase in the middle (250-600 ms) ERF in the left side of the parietal area during the control task between the pre-operative session and three months is a more complex matter. It might be related to the P3b component, which is elicited 250-500 ms post-stimulus in temporo-parietal areas, that was originally thought to reflect attentional processes and working memory updating (Polich, 2007). This view has been recently challenged and is now seen to reflect target identification guided by working memory instead of working memory updating (Rac-Lubashevsky & Kessler, 2019). Target detection could be hypothesized to be an important part of our control task, because participants had to have a mental representation of the number one in working memory and identify the target when seen, while simultaneously inhibiting responses to wrong numbers and sustaining attention to the task at hand. So this increase in the ERFs could reflect improved target detection.

The nature and meaning of the change in the late ERF (600-1000 ms) of the frontal and parietal areas deserves special consideration. While this change could be interpreted as an improvement in frontoparietal mediated control of attention, since these areas are important for attentional functions such as shifting and selection of the stimuli (Scolari, Seidl-Rathkopf & Kastner, 2015) and also the prefrontal cortex has been studied to be critical in top-down control of attention (Rossi, Pessoa, Desimone & Ungerleider, 2009). Still, the frontal ERF of late time windows (600-1000 ms) is less extensively studied.

Surprisingly, there was an increase in the late (600-1000 ms) time window of the right occipital area during the control task. The increase in the activation of the occipital area for visual stimulus processing is expected, but the lateralization and the timing of the increase in the ERFs raises interesting questions. It could be speculated that the described changes in the ERFs reflect the improved attentional control together with information processing. The late time windows of the parietal and frontal areas represent attentional control and the late time window of the occipital area represents later visual processing of stimulus. This is in concordance with the fact that the late time window overlaps with the N700 component. N700, originating from occipito-temporal areas at 500-1200 ms, is seen as a mark of post-processing of the stimuli (Bender et al., 2010) and its amplitude has been thought to reflect how much attention is allocated for stimuli (Hecht, Thiemann, Freitag & Bender, 2016). Perhaps the increase of the late occipital area time frame could be related to improvement in attentional control. The visual modality of the stimulus could explain that the change is seen on the right side.

To sum up, the changes we observed in our data and their hypothesized reflections to aforementioned ERFs suggest that the participants' attentional functions were improved due to the assumed enhancement in the cerebral circulation after CEA. This agrees with the notion that subcortical structures are vulnerable to deficits when cerebral circulation is altered because of the long arteries and narrow arterioles supplying them with blood (Moody et al., 1990) and these structures are needed for attentional processes (Cohen, 2014). This points to the direction that CEA may have an effect on the neural correlates of attention, which was seen in our results as an increased ERFs in the late middle time window of the left side of the parietal area and in the late time windows of frontal areas in together with the changes in the occipital area in the late time windows, implying some alteration in later processing of visual stimulus.

4.2 Changes in the neural correlates of working memory

We assumed that a possible change in the ERFs during the 2-back task could be interpreted as CEA affecting the neural correlates of working memory. It should be considered that our results are difficult to interpret as attentional functions overlap with working memory functions (Corbetta & Shulman, 2002). In addition, they involve partly the same brain areas: fronto-parietal activity is related to both top-down attention control (Katsuki & Constantinidis, 2014) and n-back tasks (Jacola et al., 2014; Moisala, 2017). This means that the processes are difficult to separate from each other with different tasks.

Consequently, an increase of activation in these aforementioned areas during the 2-back task would have indicated changes in the neural basis of working memory. Since working memory is reflected in the later time windows of ERFs, we expected to see changes there. Again, there were surprising results. Our results show that the mean value of ERFs during the 2-back task decreased in the right side of the occipital area in the early time windows (50-250 ms) between the preoperative and third month sessions.

It is uncertain what this change represents. It might be related to the N200 component that is seen at 200-300 ms post-stimulus, but its functional significance is unclear (Luck, 2014). This component arises from temporo-occipital areas with visual stimulus (Folstein & Van Petten, 2008) and is thought to reflect voluntary attention when processing visual information during tasks that require target detection (Suwazono, Machado & Knight, 2000). The 2-back task used in our study does not heavily require target detection, but this could indicate a change in visual information processing. It must be pointed out though, that this was the only change in the ERFs elicited by the 2-back task in our sample.

It is important to consider why the ERFs elicited by the 2-back task did not change in our sample after CEA, even though the ERFs elicited by the control task were affected. One of the reasons could be, that the hypothesized improvement of attention was not so strong that it would have affected the ERFs elicited by the 2-back task. During the control task the participants had to consciously engage attention to the numbers and react when the number one was shown on the screen. This task requires the inhibition of reaction to the wrong numbers and general alertness during the task. Thus, any changes in the ERFs during the control task could be related to the changes at the most basic level of attention. However, this presumed improvement in attentional processes might not be strong enough to have carry over effects to the highly demanding 2-back task. So, it is possible that it does not evoke the same response as it may invoke different attentional processes.

Another reason why we did not see changes in the ERFs related to the 2-back task could be, that possibly our participants did not suffer pre-operatively from cognitive deficits that would have affected their 2-back task performance and thus no benefit from CEA was possible. This is supported by the view that patients with stenosis often do not display cognitive dysfunctioning (Sztriha, Nemeth, Sefcsik & Vecsei, 2009), or the deficits are so subtle that they are not seen in daily lives (de la Torre, 2010). Also, none of the participants included in this study underwent CEA due to cognitive problems.

Even though our results would indicate that CEA did not affect the neural correlates of working memory, it does not exclude that there would be changes in the behavioral level. All in all, we did not measure how well the subjects performed in the 2-back task. In a matter of fact, a preliminary study in the CEAMEG project showed that there was significant improvement in working memory performance at the neurobehavioral test level; the participants' performance improved in Digit Span and symbol digit modalities tests (Kukkonen et al., 2019). Moreover, as the CEAMEG project was reinforced with two additional participants, Trail Making Test B (TMT-B) shows almost statistically significant improvement (p = .051) (Unpublished data). This collaborates with the previous result that performance in the n-back task and clinically used Digit Span working memory tests does not correlate (Miller et al., 2009). Furthermore, the n-back and clinical tests differ in their modalities (e.g., the clinical measurement of the Digit Span is verbal) so they depend partly on different brain areas. The weak correlation between performance in n-back and the Digit Span test may lay on the fact that the former is visually presented and relies on the use of mental imagery and the latter is aurally presented (Miller et al., 2009). So, it can be speculated that our paradigm did not elicit the same neural correlates as clinically used working memory tests. On the other hand, the result that there was change in the ERFs of control task that would indicate improvement in general attention is concordant with the fact that the performance of the subjects improved in the TMT-B, which measures attention, visual searching (Strauss, Sherman, & Spreen, 2006) and executive control (Watts, Ahern, Jones, Farrer & Correia, 2019).

4.3 Effects of the type of the task and long lasting effects

Our second question examined whether the change seen in the brain's electrical activity was different over time depending on the type of the task (2-back, control). We did not find any evidence supporting this. However, the 2-back task elicited systematically larger ERFs than the control task in the left side of the occipital area in the middle ERF and in the right side of the occipital area in the middle and late ERF during all sessions.

It is not surprising that the cognitively demanding 2-back task, a task which requires updating, manipulating and monitoring of information (Owen et al., 2005) in addition to requiring various brain areas (Jacola et al., 2014; Moisala, 2017) involving working memory evoked a stronger response than the control task. However, the brain areas where these were seen (the left and right sides of the occipital areas) do not exactly represent the areas where the 2-back condition is expected to show larger ERFs than the control task, as the n-back condition has been studied to activate dorsolateral prefrontal and parietal regions, while prefrontal activity increases as memory load increases (Jacola et al., 2014; Moisala, 2017). However, the posterior areas process perceptual information during working memory tasks, (Eriksson et al., 2015) and this could be associated with the larger ERFs from these areas. Yet these stronger ERFs are seen in the middle (250-600 ms) and late (600-1000 ms) ERFs, which indicates that the activity is not solely perceptual, but it could be related to post-processing of stimulus, since the latter overlaps with N700. To conclude, the 2-back task seems to engage these areas more actively than the control task, resulting in larger ERFs in these areas.

Lastly, we studied if the CEA had effects on the brain's electrical functioning that could be seen as late as one year after the CEA. Only a few studies have employed a follow-up time as long as one year (Plessers et al., 2014), so our study gives some insight on the permanence of these changes. In fact most of the results we found suggest that CEA could have lasting outcomes. The changes in the brain activity during the control task in the left side of the frontal and parietal areas were visible after one year of the operation. The changes in the right side of the occipital area during the control task were visible at three months and one year after the operation. During the 2-back task the changes in the right side of the occipital area were observed at three months after the operation. These aforementioned results suggest that CEA had lasting effects on the neural correlates of attention.

4.4 Strengths and weaknesses of this study

The main contribution of our work is identifying research questions for future studies. We also gained insight on the applicability of ERFs in this field, as previous work on working memory done with MEG has concentrated on oscillations. This is also the first study to our knowledge that employs MEG as a method for examining the neural correlates of working memory and attention after CEA. In addition, we contributed to investigate if the effects of CEA have long lasting effects on these functions by using a one year follow-up time.

A major limitation of our study was the very small sample size, since it is difficult to find participants in studies which compare the pre- and post- effects of surgical treatments, a common problem in clinical studies. In addition, the second major limitation in our study is the fact that we did not have a control group in our study, because finding suitable participants that could be compared with our participants undergoing CEA and the measurements required for this study was challenging. Consequently, our research cannot address the impact of co-founding factors, such as learning effects and the influence of normal ageing that could have affected our results. Moreover, we cannot know how representative our sample is, as we have not examined the characteristics of our participants’ in terms of educational level and primary cognitive functioning.

Also, when we inspected the data visually, we found out that the variance between the participants was very large in the frontal and parietal areas one year after the operation. Visualization of the raw data indicated that this variance was mostly due to one participant. This deviant data can be particularly observed in the both frontal areas in the late time window (600-1000 ms), in addition in the right side of the parietal area in the middle (250-600 ms) and late (600-1000 ms) time windows. The quality of the data for one subject was questionable and therefore interpretations regarding these brain areas and time windows must be considered with a certain caution. It could be that the hypothesizations made from the frontoparietal areas regarding the changes associated with the neural mechanisms of attention are not on a solid ground. However, the data from the occipital areas was of significantly better quality than the data from the parietal and frontal areas. This suggests that the assumptions made regarding the late processing of visual stimuli are more reliable. Consequently, statistical interpretations of the data were only possible after bringing the extreme outliers near the normal distribution's tail. This means that we could have brought actual and real observations from participants' data near the normal distribution's tail, which could have distorted the statistical interpretations. Taking all these aforementioned things into consideration, the statistical results of this work should be considered merely as indications for future research.

4.5 Future work

Our study indicates that studying the oscillations and neurobehavioral performance together may give a better insight how working memory and its neural correlates are affected by CEA and using MEG makes it possible to understand the phenomena. So it is possible that ERPs or ERFs are not the most suitable method for studying working related neural correlates, but they are more applicable to studying sensory functions, such as visual information processing. It is known that working memory is a phenomenon in which several brain areas activate simultaneously and this is commonly studied with frequency-domain analysis methods. The preliminary analysis of CEAMEG data has shown that there are postoperative changes either in the peak amplitude or peak frequency of the alpha oscillation (Kukkonen et. al., 2019). Alpha oscillations are related to working memory as well as attention, so this could be a possible consideration for future research. As the CEAMEG project continues, it might give more insights on the brain's electrical functioning and it might help understand our results better.

Some previous studies as well as ours question the value of n-back tests in measuring working memory performance. This leads to the question on what would be a suitable paradigm to capture the phenomenon of working memory while working with the practical limitations of MEG measurements. Future studies should also administrate the usage of control groups. The control group should consist of healthy participants, because stroke has the unfortunate characteristic to predispose individuals to cognitive deficits (Lal et al., 2017). Also, the sample size should be considerably larger than in this study, to gain more reliable results.

We found marks of lateralization in terms of the activation patterns of the ERFs which were difficult to explain. The possible lateralization should be taken into consideration in future studies. It could be a result from the operation side of the CEA, so it should be also noted in the future research, as it could affect the electrical functioning of the brain, as previous studies indicate. There are some studies that have examined the possible effects of the operated side on the neuropsychological functioning with the underlying hypothesis that enhanced blood supply after CEA would be the most beneficial to the functions that are mediated by the ipsilateral hemisphere (Bossema et al., 2007). A study by Mononen, Lepojärvi and Kallanranta (1990) found that there was a connection between the side of surgery and test performance; the patients operated on the left side improved in verbal tests and the patients operated on the right side improved in performance in visual memory tests. This encouraged us to speculate whether the lateralization of brain function and operated hemisphere side could give some explanation to our results. Most (60%) of our subjects were operated from the left side and our results regarding the control task show increased electrical activity on the left side of frontal and parietal area, in addition that there were improvements in behavioral working memory tests. This may be related to that verbal tests, as they are more left side mediated tasks and that attentional control is mostly mediated by the parietal and frontal area. This could also give some insight why there was no increased activation during the n-back task, which is a more visual memory task than Digit Span and hence more mediated by the right side of the brain. However, it must be noted that we did not examine with statistical means how the operation side affected the electrical functioning on the performance in working memory tests. Also, the increase in the late time window of the right occipital region does not support this hypothesis. Further investigation into this is required to draw conclusions.

4.6 Conclusions

Despite the limitations due to small sample size, our work suggests that studying the cognitive effects of CEA deserves future research. Attentional and working memory processes overlap in many ways, so it is difficult to separate them from each other, in terms of behavioral and neural mechanisms. Even though the results of this study are uncertain in many aspects, our results suggest that CEA can affect the neural functioning of attention and working memory. To conclude, our work has identified questions for future work in addition to giving insight with MEG on how the operation could affect the neural functioning of working memory and attention.

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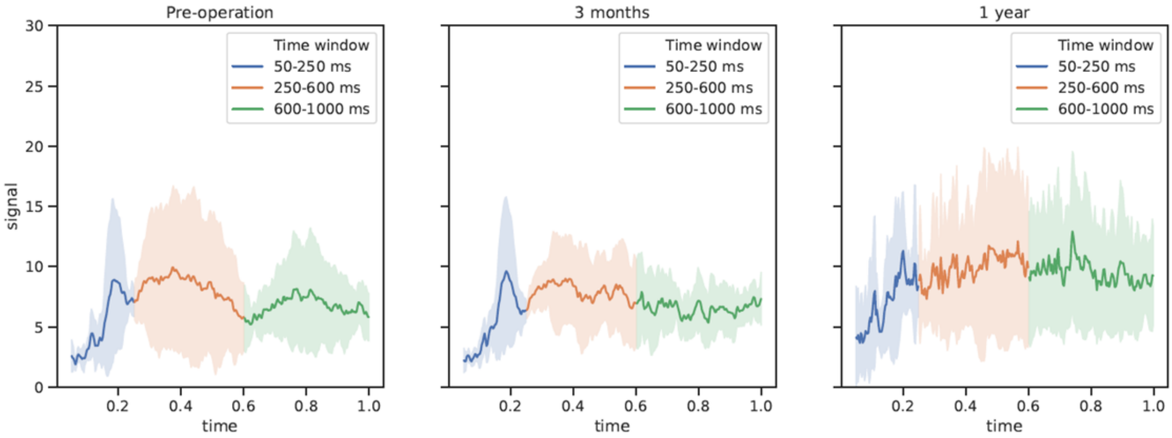
APPENDIX A

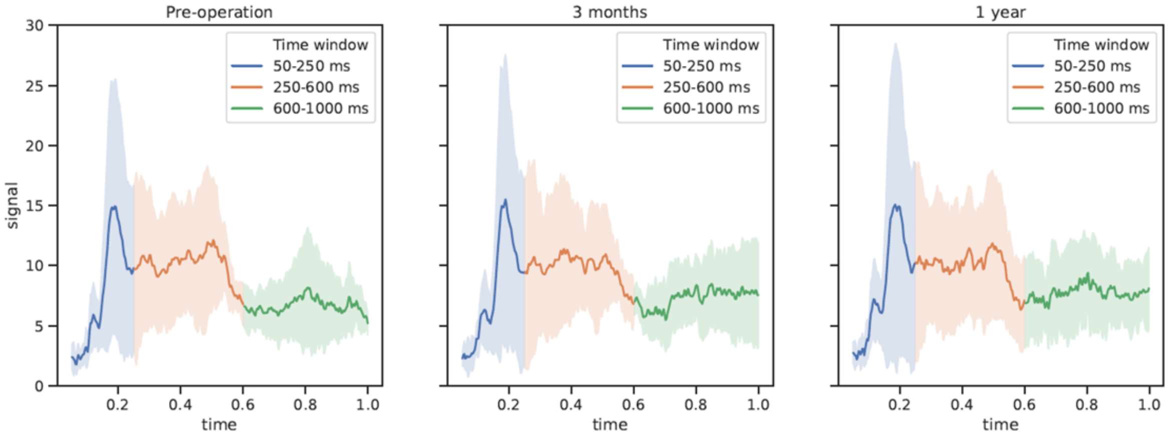
Mean values of ERFs in brain areas and time windows

Here we show the mean values of ERFs in brain areas and time windows, where statistically significant results were found. Signal represents the values of mean amplitudes while standard deviations are represented by the spread over the line.

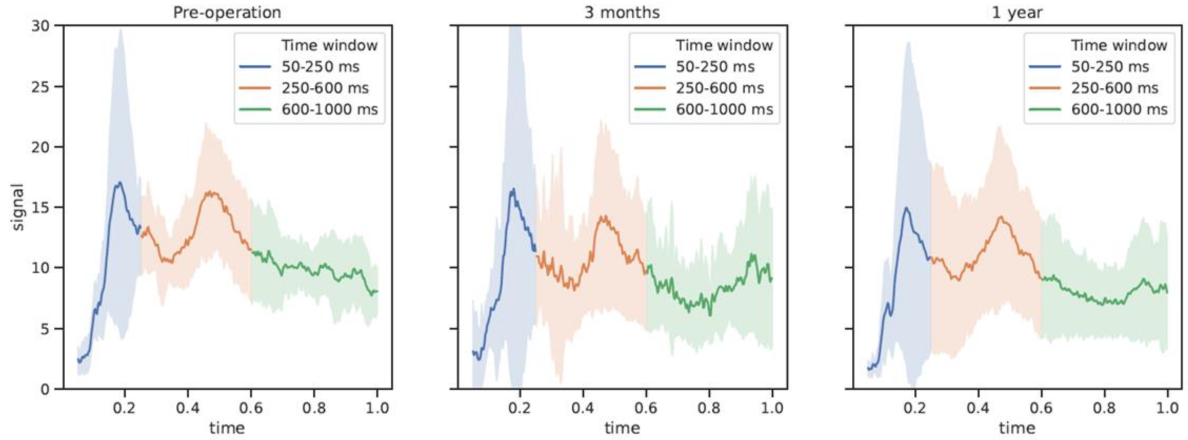
Control task left-parietal



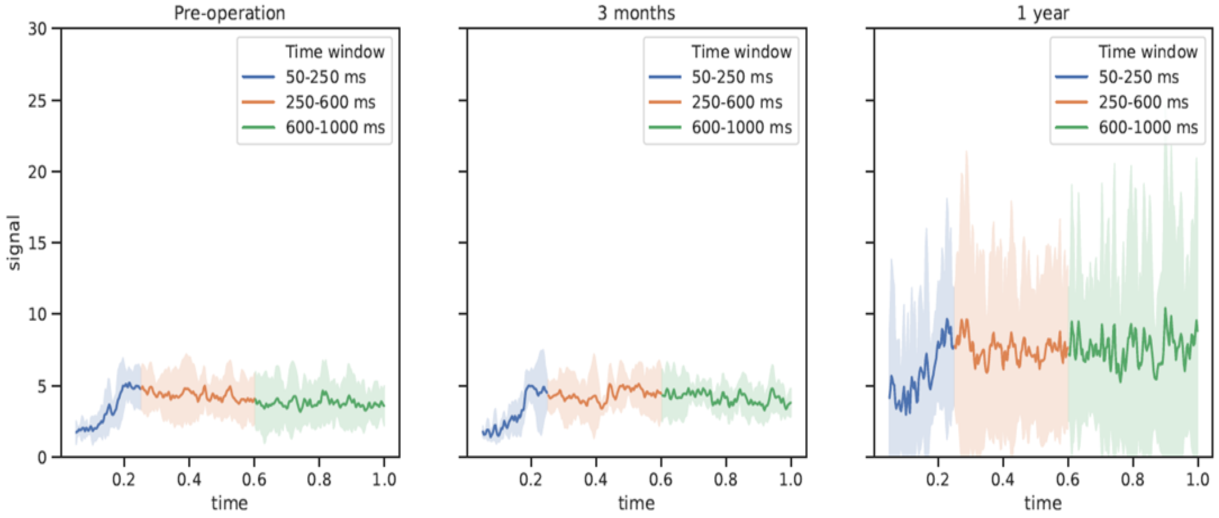
Control task right-occipital



2-back right-occipital



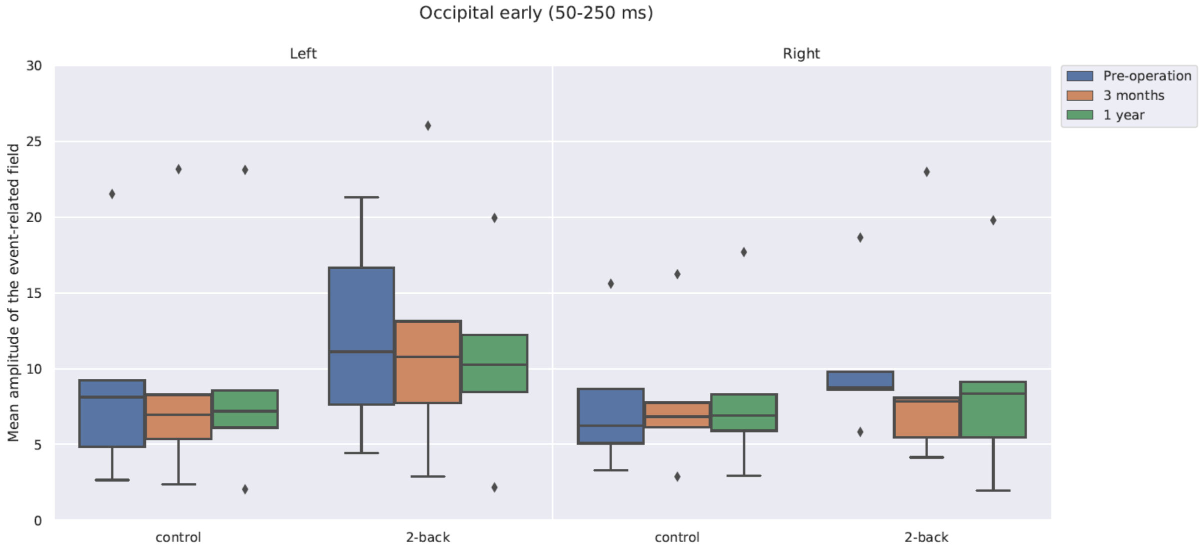
Control task left-frontal

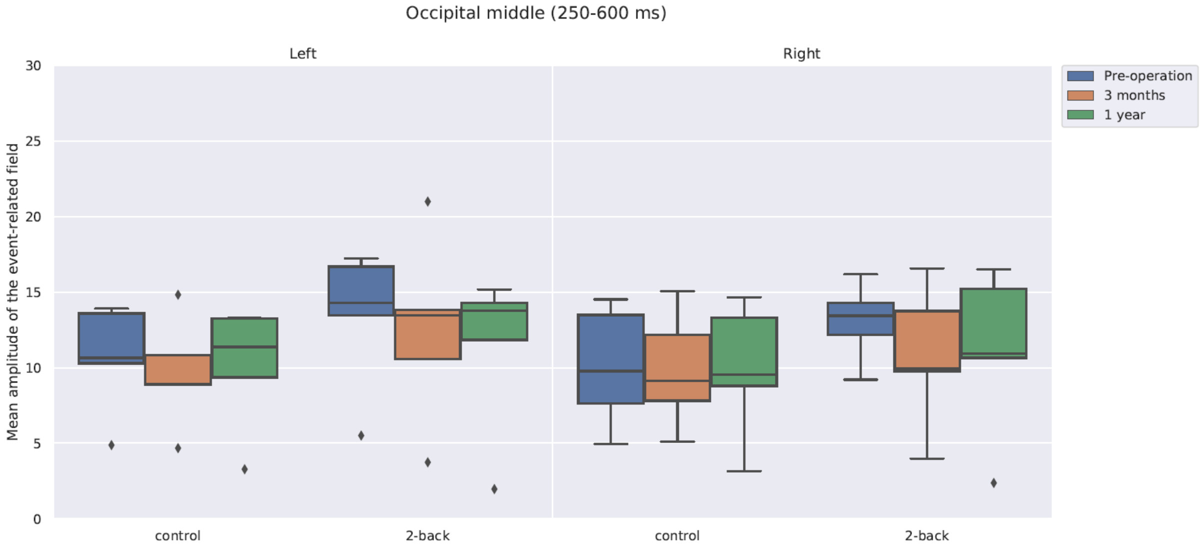


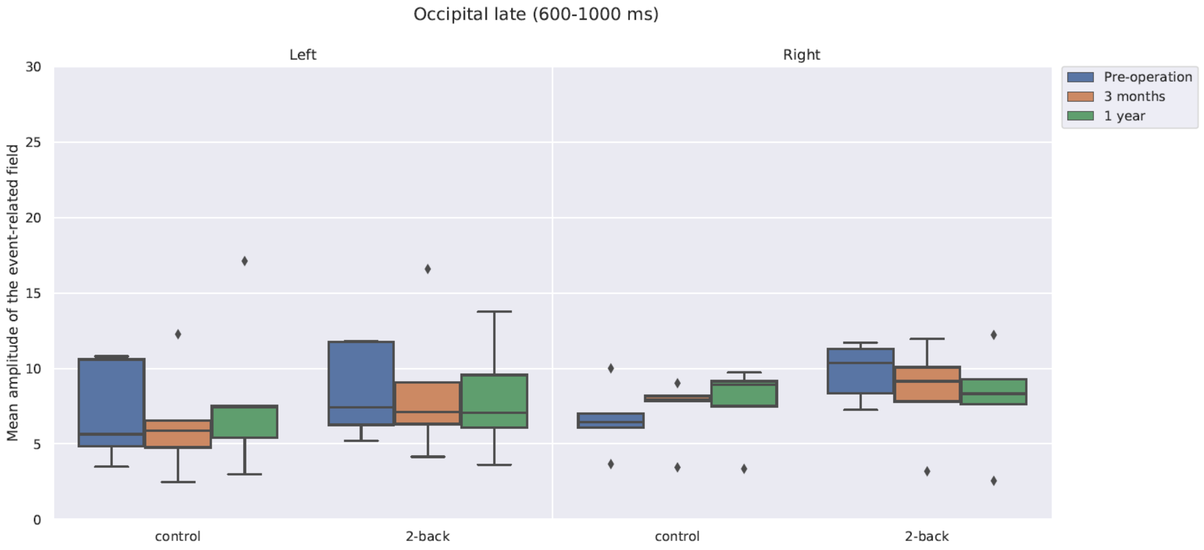
APPENDIX B

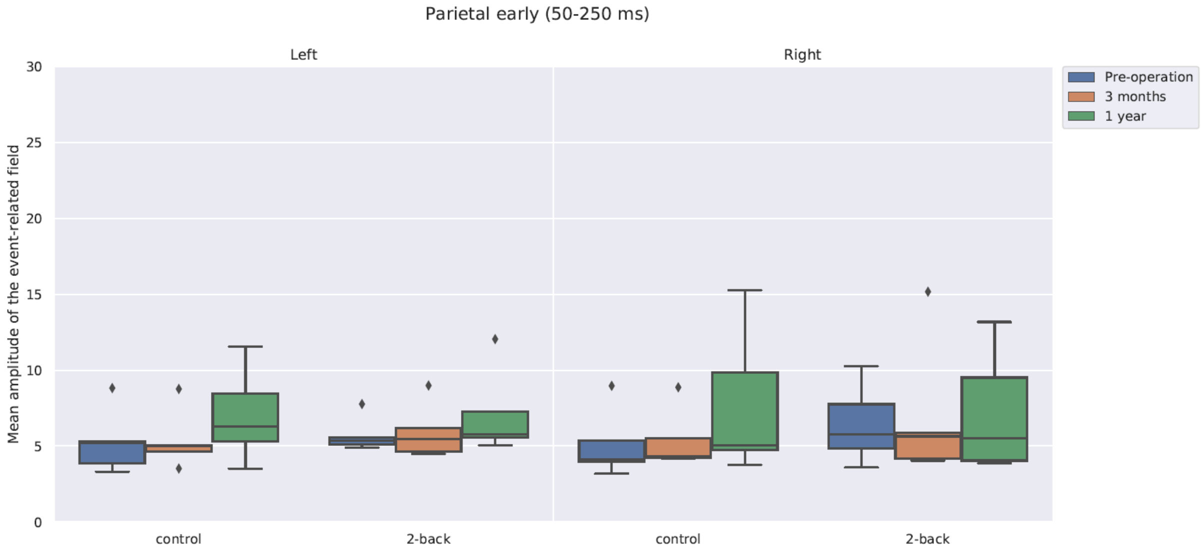
Boxplots of the mean amplitudes in the chosen brain areas and time windows

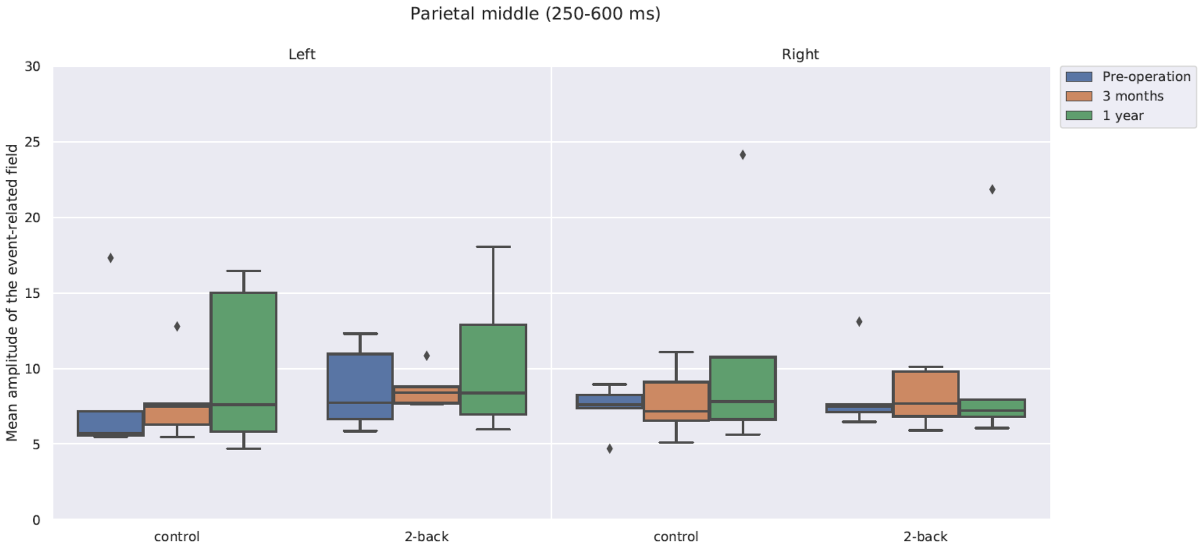
Here we present boxplots that illustrate the distribution of the mean amplitudes in the chosen brain areas and time windows. In each boxplot, the left side shows the mean amplitudes for each of the tasks separately for the left side of the chosen brain area, where the right side displays the corresponding information for the right side of the chosen brain area.

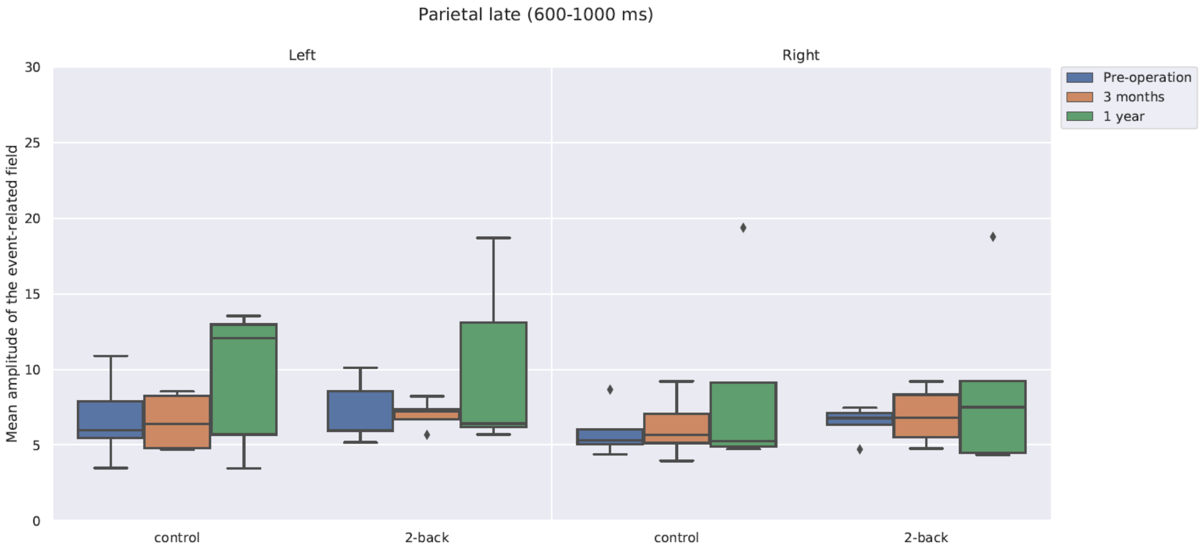


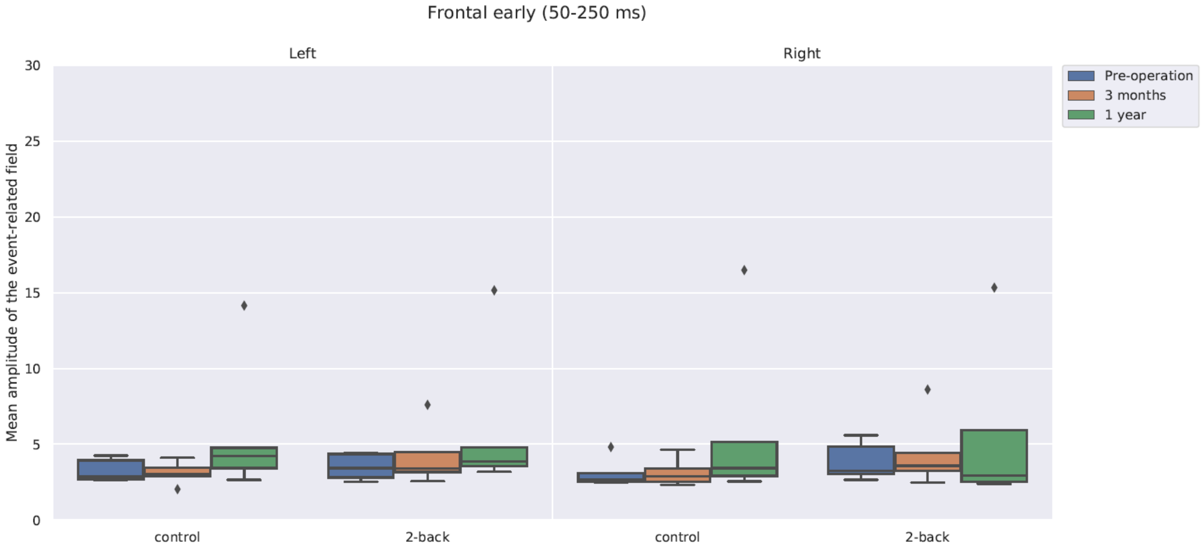


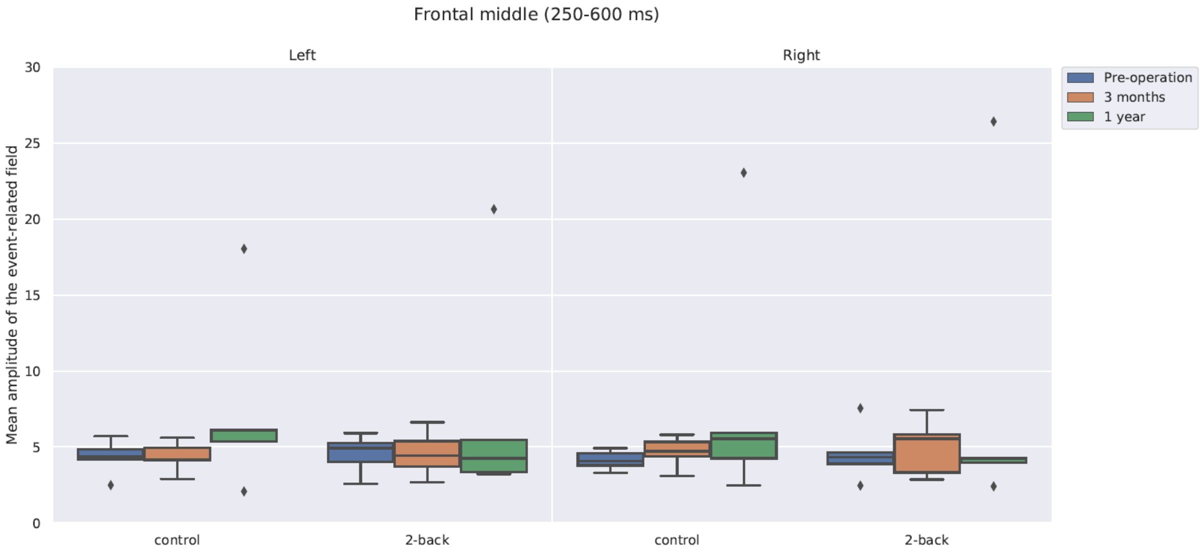

Occipital late (600-1000 ms)
Left
Right
Mean amplitude of the event-related field
0
5
10
15
20
25
30
control
2-back
control
2-back
Pre-operation
3 months
1 year

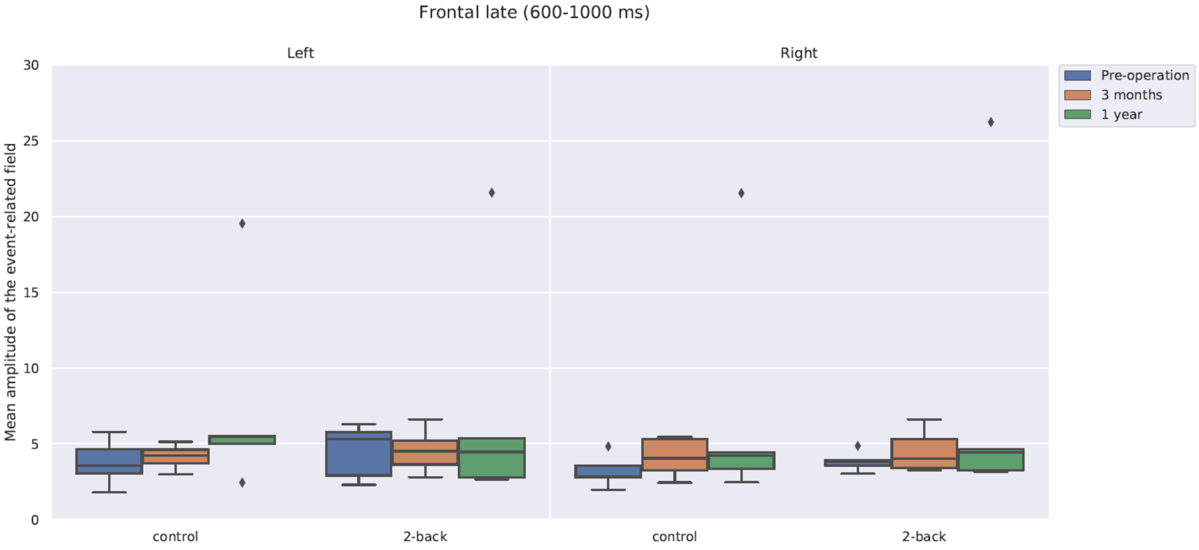

Parietal early (50-250 ms)
Left
Right
Mean amplitude of the event-related field
0
5
10
15
20
25
30
control
2-back
control
2-back
Pre-operation
3 months
1 year


Parietal middle (250-600 ms)
Left
Right
Mean amplitude of the event-related field
0
5
10
15
20
25
30
control
2-back
control
2-back
Pre-operation
3 months
1 year


Parietal late (600-1000 ms)
Left
Right
Mean amplitude of the event-related field
0
5
10
15
20
25
30
control
2-back
control
2-back
Pre-operation
3 months
1 year


Frontal early (50-250 ms)
Left
Right
Mean amplitude of the event-related field
0
5
10
15
20
25
30
control
2-back
control
2-back
Pre-operation
3 months
1 year


Frontal middle (250-600 ms)
Left
Right
Mean amplitude of the event-related field
0
5
10
15
20
25
30
control
2-back
control
2-back
Pre-operation
3 months
1 year


Frontal late (600-1000 ms)
Left
Right
Mean amplitude of the event-related field
0
5
10
15
20
25
30
control
2-back
control
2-back
Pre-operation
3 months
1 year

APPENDIX C

Descriptive statistics

TABLE 2. Descriptive statistics, effect sizes and repeated measures analysis of variance with time of measurement (preoperation, 3 months, 1 year) as within-subject factor for 2back- task.

	Preoperation		3 months		1 year				Effect size		
	M	SD	M	SD	M	SD	F	*df*	Cohen’s d[b]: M0-3	Cohen’s d[b]: M0-12	η_p^2
Left-occipital											
50-250ms	12.23	6.80	12.11	8.67	10.61	6.44	1.222	2,8	.01	.24	.23
250-600ms	13.43	4.70	12.52	6.23	13.21	1.74	.146	2,8	.17	.06	.04
600-1000ms	8.48	3.10	8.65	4.78	8.02	3.86	.107	2,8	.04	.13	.03
Right-occipital											
50-250ms	8.60	1.66	6.90	2.02	8.94	6.69	.561	2,8	**.92**	.07	.12
250-600ms	13.06	2.60	10.81	4.75	11.13	5.53	2.211	2,8	.59	.47	.36
600-1000ms	9.79	1.92	8.44	3.30	8.90	2.04	.939	2,8	.50	.45	.19
Left-parietal											
250-600ms	8.70	2.80	8.68	1.30	10.45	5.01	.972	2,8	.01	.43	.20
600-1000ms	7.14	2.10	7.03	.94	10.02	5.73	1,420[a]	1,4	.07	.67	.26
Right-parietal											
250-600ms	7.33	.58	8.07	1.84	7.20	.82	.881	2,8	.54	.18	.18
600-1000ms	6.49	1.08	6.92	1.86	8.87	5.91	.568[a]	1,4	.29	.56	.12
Left-frontal											
600-1000ms	4.51	1.80	4.55	1.47	4.25	1.50	.086	2,8	.02	.16	.02
Right-frontal											
600-1000ms	3.83	.67	4.52	1.42	4.10	.84	.567	2,8	.62	.35	.12

a) Mauchly’s test of sphericity assumption was violated, so Greenhouse-Geisser corrections were used with these values.

b) Large effect sizes (d > .8) are emphasized.

TABLE 3. Descriptive statistics, effect sizes (pre-operation vs 3 months and 1 year) and repeated measures analysis of variance with time of measurement (preoperation, 3 months, 1 year) as within-subject factor for the control task.

	Preoperation		3 months		1 year				Effect size		
	M	SD	M	SD	M	SD	F	*df*	Cohen's d[c]: M0-3	Cohen's d[c]: M0-12	η_p^2
Left-occipital											
50-250ms	9.27	7.33	6.40	2.64	6.58	2.78	1.283[a]	1,4	.52	.49	.24
250-600ms	10.66	3.63	10.01	3.69	10.11	4.15	.673	2,8	.18	.14	.14
600-1000ms	7.07	3.40	5.33	1.81	6.26	2.09	1.760	2,8	.64	.29	.31
Right-occipital											
50-250ms	7.77	4.79	6.32	2.07	6.60	2.38	.800[a]	1,4	.39	.31	.17
250-600ms	10.08	3.99	9.85	3.87	9.89	4.50	.065	2,8	.06	.04	.02
600-1000ms	6.04	1.38	7.99	.73	7.73	2.58	4.003	2,8	**1.77**	**.82**	.50
Left-parietal											
250-600ms	6.40	1.13	6.98	1.07	9.92	5.44	2.236[a]	33,15	.53	**.90**	.36
600-1000ms	6.73	2.81	6.53	1.84	9.54	4.63	2.725	2,8	.08	.73	.41
Right-parietal											
250-600ms	7.84	.77	7.81	2.33	8.36	2.42	.461	2,8	.01	.29	.10
600-1000ms	5.89	1.66	6.20	2.02	8.68	6.25	1.050[a]	1,4	.17	.61	.21
Left-frontal											
600-1000ms	3.76	1.53	4.13	.83	5.40	.41	5.385*[b]	2,8	.30	**1.47**	.57
Right-frontal											
600-1000ms	3.33	1.06	4.09	1.30	3.89	1.00	2.734	2,8	.64	.54	.41

a) Mauchly's test of sphericity assumption was violated, so Greenhouse-Geisser corrections were used with these values.

*b) Statistical significance was interpreted as following: * p < .05*

c) Large effect sizes (d > .8) are emphasized.

TABLE 4.. F-values and estimates of effect sizes from repeated measures analysis of variance with the time of measurement (preoperation, 3 months, 1 year) as a within-subject factor and the type of the task as a grouping variable.

	Main effect of the time of measurement	Effect size η_p^2	Main effect of the type of memory task	Effect size η_p^2	Interaction effect of carotid endarterectomy*memory task	Effect size η_p^2
Left-occipital						
50-250ms	F(1,4) = 2.675^{a}	.40	F(1,4) = 7.142	.64	F(1,4) = .547^{a}	.12
250-600ms	F(2,8) = .327	.08	F(1,4) = 17.335*^{b}	.81	F(2,8) = .056	.01
600-1000ms	F(2,8) = .339	.08	F(1,4) = 5.820	.59	F(2,8) = 1.292	.24
Right-occipital						
50-250ms	F(2,8) = 1.394	.26	F(1,4) = 7.460	.65	F=1,4) = .236^{c}	.06
250-600ms	F(2,8) = 1.406	.26	F(1,4) = 22.318**^{b}	.85	F(2,8) = 2.336	.37
600-1000ms	F(2,8) = .576	.13	F(1,4) = 11.980*^{b}	.75	F(2,8) = 2.372	.37
Left-parietal						
250-600ms	F(1,4) = 1.874^{a}	.32	F(1,4) = 5.425	.58	F(1,4) = .976^{a}	.20
600-1000ms	F(2,8) = 2.092	.34	F(1,4) = .183	.04	F(2,8) = .003	.00
Right-parietal						
250-600ms	F(2,8) = .306	.07	F(1,4) = .286	.07	F(2,8) = 1.007	.20
600-1000ms	F(1,4) = .827^{a}	.17	F(1,4) = .329	.08	F(2,8) = .112	.03
Left-frontal						
600-1000ms	F(2,8) = .810	.17	F(1,4) = .001	.00	F(2,8) = 3.545	.47
Right-frontal 600-1000ms	F(2,8) = 1.421	.26	F(1,4) = 1,353	.25	F(1,4) = .138^{a}	.03

[a)] *Mauchly's test of sphericity assumption was violated, so Greenhouse-Geisser corrections were used with these values.*

[b)] *Statistical significance was interpreted as following: * p < .05, ** p < .01*