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Magnetoencephalography, Diffusion Tensor Imaging and Transcranial Magnetic Stimulation in Managing Cognitive Behavioral Changes after Intracranial Vascular Surgery

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Abstract

Some frontal and temporal lobe areas are known to be part of the limbic system. The prefrontal, orbitofrontal and basal forebrain nuclei are examples of frontal lobe anatomical structures that have direct connections with the hippocampus, amygdala and basal ganglia component of the limbic system. The cognitive functions that are associated with these areas are memory, behavior and attention. Surgical clipping of a ruptured intracranial anterior circulation aneurysm would require some manipulation or retraction force applied to these regions and with concurrent presence of cisternal hemorrhages, brain edema and swelling, neurocognitive impairment is likely. By using state of the art technique in magnetoencephalography (MEG), diffusion tensor imaging (DTI) and standard neuropsychological assessment tools, gross abnormalities in brainwave morphology, contour of white matter fibers and neuropsychological scores were detected. Appealingly, these abnormalities were also used to rehabilitate the cognitively impaired individuals by using neuro-navigation guided transcranial magnetic stimulation (TMS) and utilizing stimulatory (fast) and inhibitory (slow) mode of the repetitive stimulation.

Key Words: cognition, neuro-behavior, aneurysm, magnetoencephalography, MEG, diffusion tensor imaging, DTI, transcranial magnetic stimulation, TMS

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Introduction

Neurological impairment can manifest in different ways following subarachnoid hemorrhage (SAH) and surgery of ruptured brain aneurysm. There have been some documented cases of patients in the past with long term cognitive behavioral changes after intracranial aneurysm surgery. Some patients were noted to appear grossly

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unaffected in the early stages, however, gradual deterioration in their cognitive behaviors became more evident later on (Ogden *et al.,* 1990; Richardson, 1991). More recent studies on this subject made inconclusive remark on whether the cognitive impairment was due to the SAH or the surgery itself (Al-Khindi, 2010; Hillis *et al.,* 2000). Mavaddat et al. (2000) studied 31 patients with ruptured anterior communicating artery (ACOM) aneurysms and noted that these patients demonstrated true high-risk behaviors which were thought to be due to surgery-induced injury to the orbital prefrontal cortex or frontal ventromedial limbic circuit. In our paper we discuss two patients with cognitive behavioral changes following SAH and surgical clipping of intracranial aneurysm who were evaluated with magnetoencephalography (MEG), diffusion tensor imaging (DTI) related to magnetic resonance and neuropsychological assessment. In addition, they also had transcranial magnetic stimulation (TMS) rehabilitation guided by these advanced MEG and DTI techniques.

Materials and Methods

Clinical case 1

A 59-year-old lady presented with throbbing headaches associated with nausea and vomiting. Patient was alert, conscious, orientated and her neurological examination was unremarkable. Her head CT images showed diffuse SAH with ventriculomegaly. CT angiogram identified a ruptured ACOM aneurysm as source of bleeding (Figure 1A-B).

The patient was subsequently scheduled for an emergency craniotomy and clipping of aneurysm, however on the same day of admission, her Glasgow Coma Score (GCS) dropped from 15 to 5. Therefore, she was intubated and a repeated head CT scan showed worsening hydrocephalus. The patient then underwent emergency craniotomy and clipping of the aneurysm which was uneventful. After the surgery, her condition improved with a GCS of 14. However, she was noticed to be quiet and withdrawn during the course of her post-operative recovery. Neuropsychological assessment of the patient revealed significant abnormalities in Wechsler Abbreviated Scale of Intelligent (WASI), Wechsler Memory Scale (WMS), Rey Auditory Verbal Learning, Benton Visual Retention and Comprehensive Trail Making Tests (Table 1).

She subsequently underwent brain MRI-DTI and MEG which showed abnormal configuration of the white matter fibers and low brainwave energy at both frontal lobes (Figure 1C, D, E). Therefore, she was treated with frontal lobes fast repetitive TMS (stimulatory) rehabilitation for almost a month. Her condition improved significantly after receiving TMS.

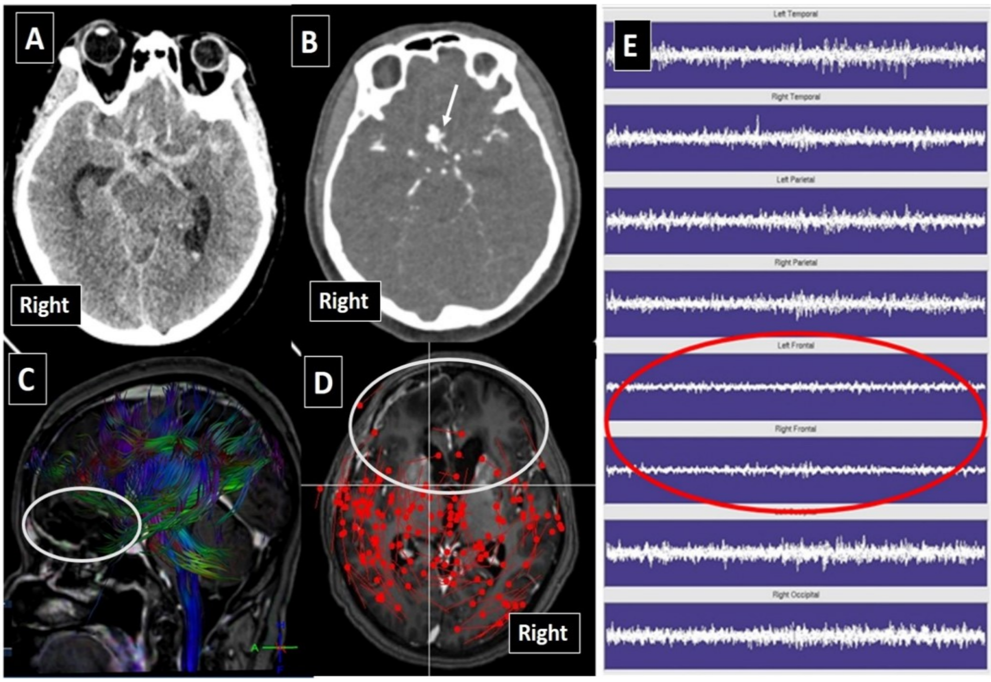

Figure 1. An ACOM aneurysmal SAH and low brain energy. A: Head CT images showed diffuse SAH. B: ACOM saccular aneurysm demonstrated on CT angiography (white arrow). C: post-operative DTI depicted lack of the orbitofrontal white matter fibers (white circle). D: post-operative MEG spontaneous brainwave analysis overlaid onto the brain MRI axial image. The red dotes indicated tabulation of the active pathway during the scan. The collection of events (red dotes) demonstrated lack of brain activation in the bilateral frontal lobes (white circle). E: MEG results also indicated lower amplitude or energy for both frontal lobes (red circle).

Clinical case 2

A 65-year-old man who was an active smoker with a medical background of hypertension, diabetes and hypercholesterolemia was brought to our hospital following a sudden onset of loss of consciousness. His GCS on admission was 14. The head CT scan disclosed diffuse SAH and cerebral angiography revealed a ruptured right supra-clinoid internal carotid artery (ICA) aneurysm (Figure 2A and B).

Later that day, the patient underwent craniotomy and clipping of the aneurysm (Figure 2C). The operative and post-operative courses were uneventful and the patient had a speedy recovery. However, during his outpatient follow-up visit, he was found to have emotional lability, poor concentration and worsening explicit memory. Neuropsychological assessment revealed extremely low score for the Wechsler Abbreviated Scale of Intelligent (WASI) and moderate to severely impaired Dementia Rating Scale (DRS) for attention and memory (Table1). This patient had right frontal lobe repetitive TMS rehabilitation (inhibitory) which was based on his abnormal contour of right frontal lobe white matter fibers (Figure 2D, E and F) and abnormally higher energy brainwaves detected on the MEG (Figure 2G, H and I). His previously abnormal cognitive parameters improved after a month of repetitive TMS rehabilitation.

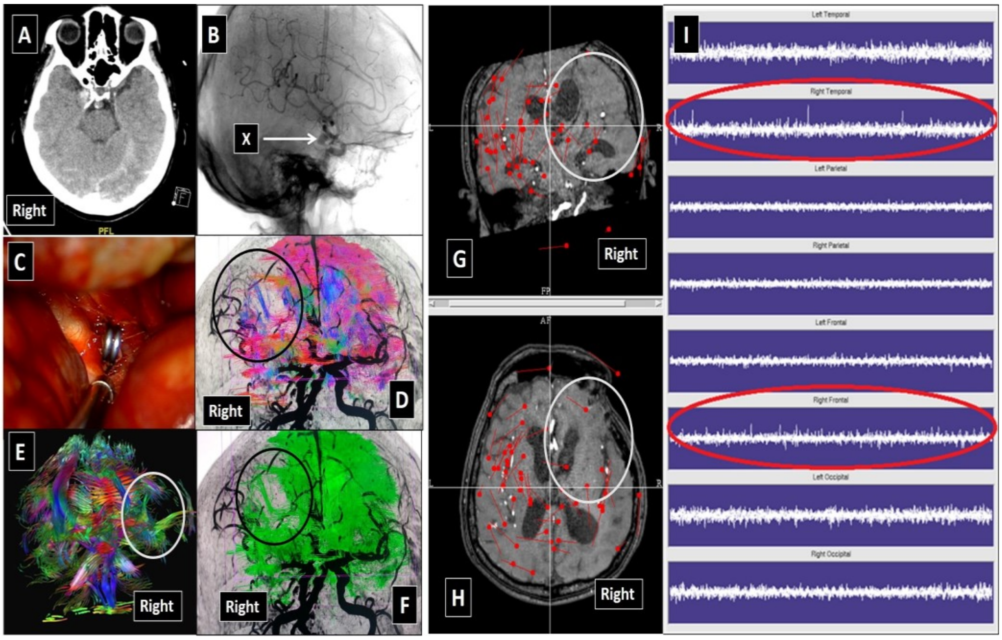

Figure 2. A right supra-clinoid ICA aneurysmal SAH and irritative energy. A: Head CT images showed diffuse SAH. B: cerebral angiography disclosed presence of right supra-clinoid ICA aneurysm (x). C: Intraoperative clipping of the aneurysm with retracted frontal lobe and SAH. D, E and F: post-operative DTI depicted lack of right frontotemporal white matter fibers when compared with the left (white and black circles). G and H: post-operative MEG study revealed lack of spontaneous brainwave activity over the right frontotemporal region (white circles). I: MEG-brainwave analysis demonstrated irritative high energy waves over the right frontotemporal region (red circle).

MEG data processing and repetitive TMS

MEG data were collected using a 306-channel Vector-view system (Elekta Neuromag, Helsinki) in a light Elekta-Neuromag magnetically-shielded room with eyes open. A magnetometer and two orthogonal planar gradiometers were located at each of 102 positions. Vertical and horizontal eye movements were recorded using paired electrooculogram (EOG) electrodes. Four head position indicator (HPI) coils were used to monitor the head position. A 3D digitizer (Fastrak Polhemus Inc., Colchester, VA) was used to record the three-dimensional locations of the HPI coils and approximately 200 head points across the scalp and three anatomical fiducial points (i.e. the nasion and left and right pre-auricular points). Data were sampled at 1000 Hz and pre-processed using Max-Filter software (Elekta-

Neuromag, Helsinki) with movement compensation. Spontaneous MEG-brainwaves analysis was made using the provided spontaneous event MEG-software. An MRI image was also collected from both patients using 3-tesla magnetic resonance imaging (MRI) system (Philips Achieva 3.0T X-series) which was fused with the MEG images (Figure 1D; Figure 2G and H). For neuro-rehabilitation, the repetitive TMS was employed. The MRI-DTI and MEG images were fused and incorporated into the TMS system for proper neuro-navigation. The prescribed TMS parameters were: fast repetitive (stimulation: > 5Hz) for the first case and slow repetitive (inhibition: < 1 Hz) for the second case at frequency range of 0-10 Hz, at 80% of motor threshold and five sessions per week for the duration of a month.

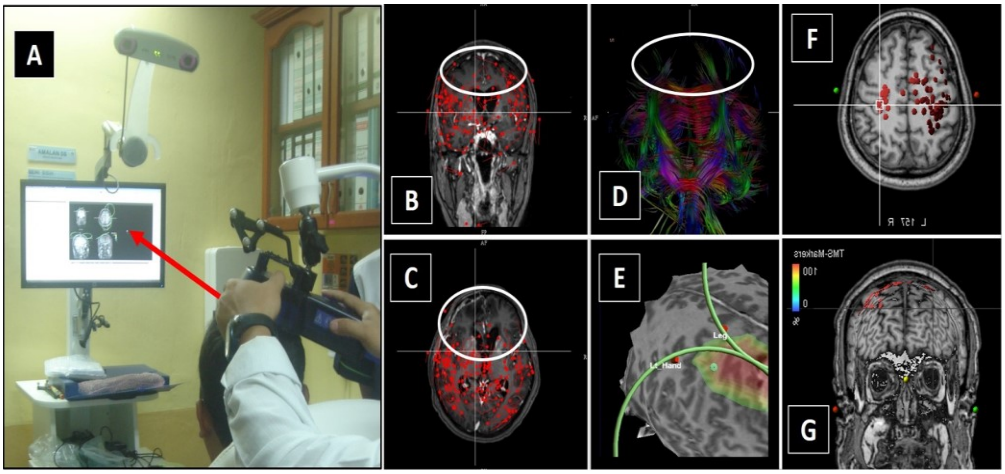

Figure 3. Neuronavigation guided TMS. A: Neuroimages guided TMS in our rehability centre. B, C and D: MEG and DTI images guided region of interest (white circles). E, F and G: Repetitive TMS (stimulatory) administered to the frontal lobes.

Results

Both of our patients had cognitive decline and behavioural changes following the SAH event and aneurysm clipping procedures. The behavioral changes in these two patients were opposite. The woman described in Case 1 was found to be more withdrawn and less talkative post-operatively and her MEG results showed decreased activity in the frontal lobes bilaterally (i.e. low brainwave energy) (Figure 1D and E). She was also found to have deterioration in her cognitive abilities, auditory and visual memory. The patient in Case 2 also had significant changes in behavior, however, instead of being more passive, he was more expressive and talkative. His DTI data analysis showed abnormal right frontotemporal white matter fibers; and MEG revealed changes in the right frontal and temporal lobes brainwave activity (i.e. more energy) (Figure 2G, H and I). Nonetheless, both of these patients who had significant decline in cognition improved after receiving repetitive TMS rehabilitation (Figure 3, Table 1).

Table 1. Neuropsychological tests after the surgery and after TMS.

Case 1	Post-surgery	Score classification	Post-TMS	Score classification
	Wechsler Abbreviated Scale of Intelligent (WASI)	Extremely low	Wechsler Abbreviated Scale of Intelligent (WASI)	Borderline
	Wechsler Memory Scale (WMS)	Extremely low	Wechsler Memory Scale (WMS)	Extremely low
	Rey Auditory Verbal Learning Test	Below average	Rey Auditory Verbal Learning Test	Below average
	Benton Visual Retention Test	Below average	Benton Visual Retention Test	Below average
	Comprehensive Trail Making Test	Severely impaired	Comprehensive Trail Making Test	Mildly to moderately impaired
Case 2	Post-surgery	Score classification	Post-TMS	Score classification
	Wechsler Abbreviated Scale of Intelligent (WASI)	Extremely low	Wechsler Abbreviated Scale of Intelligent (WASI)	Borderline
	Dementia Rating Scale (DRS) - Attention	Moderately impaired	Dementia Rating Scale (DRS) - attention	Moderately impaired
	Dementia Rating Scale (DRS) - Memory	Severely impaired	Dementia Rating Scale (DRS) - Memory	Moderately impaired

Discussion

Neurological deficits, especially cognitive impairments are not uncommon after intracranial surgery. Stenhouse et al. (1991) did a study on patients with ACOM aneurysm ruptures where these patients on average were noted to have intelectual and memory deterioration. Buckner et al. (1996) demostrated in his experiment that the visual and auditory memory pathways involved the fronto-opercular cortex, anteror cingulate, right anterior prefrontal cortex, medial frontal cortex and motor cortex of the frontal lobes. Consistent with these findings, the abnormal frontal lobe fibers demonstrated in our patients likely contributed to the deterioration in their memory and cognitive functions. Pertaining to MEG, our MEG-brainwave analysis revealed brain activation with disorganized pattern following aneurysmal subarachnoid hemorrhage. Reduced activation was noticed in cingulate gyrus, frontal lobe and areas that were likely retracted during the surgery. These electrophysiological changes in MEG correlated with the structural changes shown on DTI and resembled the electropathological mechanism that explained cognitive difficulties among patients with aneurysmal subarachnoid hemorrhage. Noteworthy that no specific electropathological mechanism leading to cognitive difficulty was identified before in SAH. However, the correlating factors that were described in literature to be associated with cognitive impairment in SAH were poor initial neurological status, subarachnoid blood volume, vasospasm, spreading cortical depression, ischemic complication, hydrocephalus, seizure and aneurysm location (Al-Khindi, 2010). According to Orbo et al. (2008), acute clinical factors such as aneurysmal SAH severity and thickness of subarachnoid blood (Fisher grading) were not primary determinants of cognitive outcome. It was hypothesized that secondary complications such as vasospam and increased intracranial pressure may play larger roles in determining the cognitive outcome.

Recent research suggested that SAH may actually affect the brain at a microscopic, synaptic level. Tariq et al. (2010) used rat models of SAH and found that SAH disrupted long-term potentiation in the limbic system which was a process thought to underlie memory and learning. Concerning aneurysm surgery, it was suggested that the long term cognitive sequelae may have resulted from the effects of brain surgery, such as prolonged anaesthesia, temporary regional cessation of blood low, brain retraction, use of antiepileptic medications or even more general effects of bed rest and debility rather than the SAH alone. The frequency or severity of cognitive deficits may be associated with particular aspects of surgical management and might be reduced by changes in protocol to provide neural protection or aimed at avoiding hypoperfusion, hypoxia or damage to eloquent brain regions (Ljunggren, 1985).

To gain improvement in cognition after intracranial vascular surgery, TMS rehabilitation should also be offered to patients. Our two patients showed obvious improvement in cognition after a month of aggressive repetitive TMS. TMS is considered to work in opposition to MEG. Rather than detecting the magnetic signals, it emits fast and strong magnetic pulses (Tesla) to induce and modify the cortical activity. The electromagnetic coil placed on the scalp emits a time-varying magnetic field that last for 100-200 microseconds. The strength of the magnetic field is about 1.5-2 tesla at the coil surface. It induces current flow in neural tissue and membrane depolarization. Thus, the physiological effects depend on the site, network, mode, frequency and duration of the stimulation. Fast repetitive TMS using > 5Hz has a stimulatory effect (used in case 1) whilst slow repetitive TMS of $\leq$ 1Hz has an inhibitory effect (used in case 2). In our setting both the MEG and MRI-DTI are combined with navigated TMS to select and approach the dysfunctional brain area for TMS rehabilitation.

Conclusion

Cognitive behavioral impairment is one of the serious sequelae from aneurysmal SAH. It affects the quality of life of patients by causing abnormal behavior, memory and focus-learning impairment. MEG and DTI can be employed as effective tools to investigate the aetiology of cognitive impairment after intracranial vascular surgery. MEG and DTI data can also be incorporated into the TMS system to facilitate with navigating the area of interest for the non-invasive neurorehabilitative therapy.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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