Increased Frontal Lobe Activation After Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—Neurocognitive deficits are common among survivors of aneurysmal subarachnoid hemorrhage, even among those with good outcomes and no structural lesions. This study aims to probe the neurophysiological underpinnings of cognitive dysfunction among patients with ruptured intracranial aneurysms using magnetoencephalography (MEG).

Methods—Thirteen patients who had undergone uncomplicated coiling for aneurysmal subarachnoid hemorrhage and 13 matched controls were enrolled. Neuropsychological tests were done before magnetoencephalography scans. Magnetoencephalography data were acquired in a 151-channel, whole-head magnetoencephalography system for resting state and 2 cognitive tasks (go-no-go and set-shifting). Mean time from treatment to test was 18.8 months.

Results—Cognitive tasks of inhibition (go-no-go) indicated greater activation in the right anterior cingulate and inferior frontal gyrus, and cognitive set-shifting tasks (mental flexibility) indicated greater activity in the bilateral anterior cingulate cortex and right medial frontal gyrus among aneurysmal subarachnoid hemorrhage patients, with significantly different timing of activation between groups. Resting-state, beta-band connectivity of the anterior cingulate correlated negatively with Montreal Cognitive Assessment scores (left: \( r = -0.56; P < 0.01 \) and right: \( r = -0.55; P < 0.01 \)); higher connectivity of this region was linked to poorer cognitive test performance.

Conclusions—We have shown increased activation in areas of the anterior cingulate gyrus and frontobasal regions during the execution of more demanding tasks in good grade. The degree of activation in the anterior cingulate gyrus has a negative correlation with cognitive (Montreal Cognitive Assessment) scores. These subtle differences may be related to the common neurocognitive and behavioral complaints seen in this patient population. (Stroke. 2016;47:2503-2510. DOI: 10.1161/STROKEAHA.116.013786.)

Key Words: aneurysm ■ executive function ■ frontal lobe ■ magnetoencephalography ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) is a medical emergency with very high morbidity and mortality rates.1–4 Advances in care have decreased mortality,5 and survival rates after aneurysm rupture are reported at 65%.6 Among survivors, ≤80% are considered to have good recovery7 using the Glasgow Outcome Scale.8 However, more sophisticated tools reveal that ≤50% have neurocognitive deficits, usually in the absence of structural lesions.20–24 In contrast to other types of stroke, aSAH affects a relatively young, productive population.6 The combination of younger age and high morbidity yields substantial long-term personal and socioeconomic burden, with estimates that ≤50% of survivors will not return to the same level of work.14,15

Impairments in memory are reported in ≤60% of survivors and executive function and language problems in 75%5,12 Deficits in visuospatial construction, memory, mental flexibility, and psychomotor speed are shown even in good-outcome patients16 and can persist beyond 1 year.7,12,17 Cognitive impairments are often more highly correlated with health-related quality-of-life scores than are physical impairments.18

The cause of neurocognitive deficits remains unknown,19 despite structural magnetic resonance imaging (MRI) investigations of lesion location and atrophy.20–24 Theories of immediate damage include diffuse injury caused by decreased perfusion at time of rupture16,25 and the presence of blood and its breakdown products in subarachnoid space.11 Injury severity and volume of subarachnoid blood have been correlated with cognitive outcomes.7,10,26 Reduced cerebral blood flow in the frontal lobes after clipping has also been correlated to cognitive function.27 Because of variable impacts of hydrocephalus, aneurysm location, treatment method, vasospasm, and ischemia on cognitive function after aSAH,10,12,16,28 a tool to describe patterns of neural activation in this population is justified. Reconstruction of white matter tracts in the vicinity...
of aneurysm rupture has been successfully performed using diffusion tensor imaging; this also suggests secondary and more diffuse changes leading to inefficient neuronal function that may impact cognitive function more than any focal structural damage.29

Limited description of functional network integrity after aSAH exists. The clinical heterogeneity and diffuse effects of aSAH suggest that functional connections can be important to understand persistent cognitive dysfunction. Recently, functional MRI work suggested neural inefficiency with larger blood oxygenation signal detected during memory tasks after aSAH.30 Magnetoencephalography combines spatial resolution paralleling that of functional MRI and high temporal resolution of electroencephalogram measurements (EEG), making it an ideal modality for exploring neurocognitive function. Magnetoencephalography (MEG) has been successfully used to elucidate underlying electrophysiological mechanisms in normal brain function and development31,32 and disease processes33–36 and mild traumatic brain injury.37,38

The aim of this study was to investigate the functional underpinnings of executive dysfunctions after aSAH using MEG. Resting-state and task-based MEG testing were used to investigate aSAH survivors with good outcomes and a cohort of matched controls. MEG tasks were selected to tap 2 frontal lobe executive functions; inhibitory control (go-no-go task) and mental flexibility (set-shifting task).

Methods
Research ethics approval was obtained. Patients with ruptured intracranial aneurysms, admitted in good grade and considered to have good outcome based on the extended Glasgow Outcome Scale39 in follow-up, were recruited. Other inclusion criteria are as follows: age ≥18 years; single aSAH with the causative aneurysm treated with uncomplicated coiling; no evidence of ischemic lesion; and no parenchymal hemorrhage.

Uncomplicated placement of external ventricular drain was not criterion for exclusion because acute hydrocephalus may not correlate with long-term, cognitive outcomes.10 Exclusion criteria were contraindication for MRI scanning, history of previous stroke, neurological or psychiatric disorders, or previous brain surgery.

Thirteen patients (9 female patients) and 13 matched controls were enrolled. Detailed demographics are provided in Table. Neuropsychological tests (Wechsler Abbreviated Scale of Intelligence; composite MOCA). Mean time from aSAH to MEG was 18.8 months (2.4–67.5; SD=19). The number of postsecondary education years (controls=1.92; SD=0.083 and aSAH=1.54; SD=0.14; t=−2.2; P=0.03) and Wechsler Abbreviated Scale of Intelligence scores (controls=66.1; SD=9.7 and aSAH=μ=56.5; SD=14.6; P=0.05, Wilcoxon rank-sum test) were different, but composite MOCA scores were not (controls=24.8; SD=3.1 and aSAH=μ=23.9; SD=3.9; t=−0.64 (23); P=0.5).

Behavioral Results
For both the inhibition and set-shifting tasks, aSAH group performed as well as controls on measures of reaction time and accuracy. For the inhibition task, there were no significant differences in reaction time (controls μ=388.0 ms; SD=64.16 ms and aSAH μ=408.6 ms; SD=67.25 ms; P>0.05) or accuracy (controls μ=97.4%; SD=2.48 and aSAH μ=96.9%; SD=2.72; P>0.05) between groups. For the set-shifting task, there was no difference on either reaction time (controls μ=775 ms; SD=30 and aSAH μ=775; SD=40; P>0.05) or accuracy (controls μ=93.2%; SD=2.6 and aSAH μ=88.3%; SD=3.5; P>0.05), although, as expected, there was a main effect of condition on both reaction time (easy μ=720 ms; SD=35 and hard μ=830 ms; SD=35; F(1,28)=77.9; P<0.001) and accuracy (easy μ=95.2%; SD=2.1 and hard μ=86.4%; SD=3.9; F(1,28)=37.1;
The easy condition had faster reaction times and greater accuracy. The interaction was not significant.

**MEG Results**

Mean, whole-brain spectral power was similar for both groups (Figure 4A), showing classic brain 1/f relationship of frequency–power content and dominant alpha peak typical of intrinsic neural oscillations. Spectrum and peak oscillatory power were similar. Graph analysis measures of mean brain strength, clustering, eigenvector centrality, and path length were calculated for all canonical frequency bands and examined (mixed effect ANOVA) to characterize network integration and segregation (Figure 2B). Significant effects of frequency were observed ($P<0.05$) for combined groups, with inverse trend (decreasing measure with increasing frequency), but without significance ($P>0.05$).

Network-based statistic group failed to identify differences in resting network topology between the groups. For qualitative comparison, spare networks for the 2% top connections were calculated (group mean connections shown in Figure 2C). Figure 1B shows between-groups image contrast results for inhibitory control. The left middle temporal gyrus showed significantly greater activation in controls at 125 to 175 and 300 to 350 ms time windows. Interestingly, greater activation in the right anterior cingulate cortex and inferior frontal gyrus was evident in aSAH patients and confirmed with virtual sensors (Figure 1C). Figure 2B highlights image contrast for extradimensional shifts, where higher activation in bilateral anterior cingulate cortex and right middle frontal gyrus ($P<0.05$) were evident in aSAH patients. Figure 2C illustrates these differences and their timing.

Given both tasks showed greater anterior cingulate cortex activation in aSAH, analysis of resting connectivity from these seed regions was conducted. Connectivity strength, clustering, and centrality of the nodes were compared across all frequency bands, and correlations between these measures and cognitive–behavioral outcomes were computed. No differences exist between groups at any frequency band ($P>0.05$). Significant negative correlations between seed connectivity strength (beta band) for the combined cohort/both groups and total MOCA score were found, with greater seed region phase synchrony with the rest of the network correlated with lower MOCA scores (left anterior cingulate cortex [ACC]: $r=-0.56$; $P<0.01$ and right ACC: $r=-0.55$; $P<0.01$). A subsequent analysis of the resting ACC connectivity strength in the beta band versus measures of accuracy and reaction
time in both tasks revealed no significant correlations, either for individual groups or when combined.

Discussion

The main findings of our study are the differences in neurological activation in frontal lobe regions (anterior cingulate gyrus and middle/inferior frontal gyrus) between aSAH patients and controls. These differences in electrophysiology were detected during execution of more demanding tasks and may underlie the electrophysiological mechanism for cognitive difficulties in this population. No specific physiopathological mechanism to explain the cognitive dysfunction has been identified, but severity of initial presentation and volume of subarachnoid blood have often been correlated with cognitive outcomes.7,10,26 The influence of other factors such as hydrocephalus, aneurysm location, treatment method, vasospasm, and ischemic complications on neurocognitive sequelae are less clear.10,12,16,28 These pathological processes are acute or subacute issues and would not be expected to lead to permanent deficits in the absence of ischemic damage to the neural tissue. However, evidence that physiopathological changes in the acute phase of aSAH do not lead to permanent functional neuronal change is unavailable. Cortical spreading depression, defined as depression of evoked and spontaneous EEG activity that spreads at low velocity through areas of the cortex,44,45 is an example of functional or electrophysiological dysfunction that can happen in the absence of an identifiable lesion and can lead to further ischemic damage in injured tissue. Massive electrophysiological changes with shifts in intra and extracellular ion concentrations and excitatory amino acid release have been demonstrated during cortical spreading depression46 and correlated with delayed cerebral ischemia, stroke, and poor outcomes after aSAH.47

Figure 2. Source localization of evoked responses from the set-shifting task. A, Experimental schematic demonstrating an example of an extradimensional (hard) shift. B, One-tailed between-group contrasts for the extra-dimensional shift. There were no regions where the controls showed greater activations than the aneurysmal subarachnoid hemorrhage (aSAH) group, although aSAH-control revealed greater activity in the right anterior cingulate cortex (ACC), right medial frontal lobe (MFG), and left ACC. C, Virtual sensor time series reconstructed from these locations demonstrate the timing of the differences between the aSAH and control groups.

Figure 3. Group comparisons of the Montreal Cognitive Assessment (MOCA) and Wechsler Abbreviated Scale of Intelligence (WASI) outcome scores.
synaptic changes. Tariq et al showed that long-term, hippocampus potentiation, a process fundamental in learning and memory, is disrupted after aSAH. They observed little neuronal damage, suggesting that the disruption is not result of cell death, but rather functional. Although our current study does not address this hypothesis, it is possible that electrophysiological dysfunction caused by aSAH also occurs in patients with better clinical grades, and in this case, it could be localized to cortical areas most susceptible to injury and last longer, perhaps with persistent changes in specific neuronal networks.

Resting-state MEG parameters showed no significant difference in mean whole-brain spectral power across frequency bands (Figure 4A). Resting-state network integration and segregation analysis and network connectivity were also similar. Therefore, at baseline, one can assume that aSAH survivors and controls share similar parameters of brain activation. However, task-based MEG revealed significant differences between groups in specific regions of the frontal lobes (bilateral anterior cingulate gyrus and right middle frontal gyrus). Patients showed increased activity in these areas during tasks designed to evaluate mental flexibility (set-shifting) and inhibition (go-no-go). These tasks measure key components of executive function, such as ability to change focus from one activity to another and to stop planned responses and inappropriate behavior (error monitoring).

A core component of executive functioning is inhibitory control, and measure of inhibitory control gives an indirect assessment of working memory function. During completion of an inhibitory task, the goal or retention of the appropriate response must remain in the working memory. Our finding of increased activity on inhibitory go-no-go tasks is in accordance with recent functional MRI work showing widespread increase in cortical activation during working memory tasks. These findings indicate inefficient neuronal firing or networking, with more activation being required to perform each task and begin to objectively describe the host of cognitive dysfunctions in the so-called good-recovery aSAH patient.

We also identified a negative correlation between connectivity of the anterior cingulate gyrus with cognitive outcomes. Greater synchrony with the rest of the network correlated with lower MOCA performance (Figure 5). Resting-state neuroelectrical activity was similar, but more demanding tasks elicited differences in neuronal activation between the 2 groups, as mentioned, suggesting inefficient
and excessive neuronal firing in certain regions. Similarly imaging studies in experimental psychology show that the efficiency of interactions between brain regions can differentiate cognitive task performance even among healthy individuals with no structural damage; slower performing individuals tend to require more prefrontal executive control than do faster individuals to perform a task successfully.\textsuperscript{51} Translated to clinical experience, these patients seem to be functioning well but struggle to cope with demands of work or school.

The ACC is associated with motor planning and cognitively demanding processes, also playing roles in affective and emotional responses.\textsuperscript{52–54} Increased activity in this complex region, involved in network modulation and integration between motor control, behavior, and affect,\textsuperscript{52,53} may be the electrophysiological phenotype for neurocognitive dysfunction in this population. We are unable to determine whether the increased activity is compensatory or because of upregulation caused by aneurysm rupture. This distinction is important because potential treatment approaches hinge on inhibition or stimulation of neural activity.

Treatment of neurocognitive deficits after aSAH is in its infancy.\textsuperscript{6,55} Evidence exists for improved executive functioning with computerized training programs designed for various populations and ages.\textsuperscript{50} However, understanding how executive functions are impaired among aSAH survivors is fundamental, so specific training and practice programs can be designed appropriately to regain essential cognitive traits. Our finding of localized neuronal activation differences in the ACC and frontobasal regions might be the first step toward developing imaging and more targeted treatment methods.

**Limitations**

In our cohort, the Wechsler Abbreviated Scale of Intelligence\textsuperscript{40} results at baseline were different between groups (\(P=0.05\)). This cannot be assumed to be because of aneurysm rupture. Although most of our participants had postsecondary education, recruitment of control participants was primarily through word of mouth at an academic institution, and the difference in terms of years of education was significant (controls>aSAH; \(P=0.03\)). We studied a selected population, and our results might not apply to more severe aSAH or patients with ischemic lesions or submitted to clipping.

**Summary**

Our investigation showed that neuronal activation in survivors of aSAH differs from healthy controls. Good-outcome patients often report neurocognitive difficulty despite absent ischemic or hemorrhagic parenchymal lesions as structural explanations. We have shown increased activation in the anterior cingulate gyrus and frontobasal regions during the execution of demanding tasks, suggestive of inefficient use of neuronal firing or connections, and that the degree of activation in these regions has a negative correlation with cognitive scores. These subtle differences may represent the electrophysiological basis for neurocognitive and behavioral complaints in this population.

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**Disclosures**

None.

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SUPPLEMENTAL MATERIAL

**MEG tasks**

Resting-state data were recorded for 5 minutes. Participants were awake but relaxed while looking at a grey ‘X’ inside a circle projected centrally on the screen (65 cm in front of the participant’s nose). The Go/No-Go is an inhibition task comprised of 2 conditions in 2 separate runs: vigilance (75% No-Go responses) and inhibition (75% Go responses). Stimuli consist of faces with a blue or purple border where colour indicates a Go or No-Go trial. Figure 1A shows a schematic of the paradigm. Faces were provided free of charge by The Research Network on Early Experience and Brain Development to be used in research experiments (www.macbrain.org). One hundred correct No-Go trials were collected for each condition.

Set-shifting Task measures mental flexibility. Stimuli consisted of three coloured shapes (2 above, 1 below) where the bottom image matched one of the top images either in shape or colour. Subjects selected which shape matched the lower one. See Figure 2A for a schematic of the task. There were two types of shifts: intra-dimensional (changes within a dimension) and extra-dimensional (changes between dimensions). The extra-dimensional shifting requires greater attention, cognitive control and mental flexibility. Three hundred and seventy trials were presented and 50 extra-dimensional shifts were acquired.

**MEG data processing**

Resting-state MEG data were band-pass filtered offline at 1-150 Hz. A notch filter (60 Hz powerline frequency, 8 Hz bandwidth) and third-order spatial gradient environmental noise-cancellation were applied. Cortical and sub-cortical sources of interest (90 locations) were identified using Automated Anatomical Labelling atlas (AAL). Time-series data were reconstructed from AAL locations using vector beamforming (linearly constrained minimum variance; LCMV) for each subject and filtered into five bandwidths: Theta (4-7 Hz), Alpha (8-14 Hz), Beta (15-30 Hz), Gamma (30-80 Hz) and High-Gamma (80-150 Hz). Beamforming applied an adaptive spatial filter allowing accurate source-level activity reconstruction and artefact suppression. Individual weight vectors were applied to each sensor measurement and summatd to give estimated source activity to a particular location.

The 5 band-pass filtered waveforms were submitted to functional connectivity analysis with weighted Phase Lag Index (wPLI). Instantaneous phase of each sample from the band-limited time-series was calculated with Hilbert transform. Degree of phase synchronization between all pairwise seed combinations was computed using wPLI. Between 0 and 1, it quantifies the degree of phase synchrony between two seed/sources (seed-seed connectivity).

Non-parametric permutation testing using Network Based Statistic (NBS) Toolbox was done to investigate group differences in connectivity (NBS:Extent and NBS:Intensity methods; initial suprathreshold t-value=2, p<0.05, 10000 permutations). Graph analysis of network segregation and integration were obtained using Brain Connectivity...
These whole-brain measures included: **node strength**: node connectivity to the rest of the network; **clustering coefficient**: functional embeddedness of a node in a network; **Eigenvector centrality**: how connected a node is to other highly connected nodes; and **characteristic path length**: a measure of network integration. Brain networks were visualized using BrainNet Viewer. Further behavioural correlation analyses were conducted using MATLAB Statistics Toolbox (The Mathworks, Inc.).

**Inhibition and set-shifting tasks** were source localized with the same parameters but through different pipelines. **Inhibition task** data were processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). MEG data were filtered offline (Butterworth bandpass filter at 1-50Hz) with trials epoched from -200 to 600ms (0=start of trial). Trials with excessive head motion (>0.5cm within or >1cm between trials) were removed. Independent Component Analysis (ICA) was used to remove any trial with eye movements and cardiac components artifacts exceeding 2000fT. Source reconstruction was performed using Single Shell Head model and eigenvalue based beamforming to solve for the inverse solution. Overlapping 50ms sliding time windows starting at 50-100ms to 400-450ms were used to identify neural sources active in each window. Volumetric beamformer images were smoothed spatially with a Gaussian kernel of 12mm and contrasted in SPM12 for statistical testing.

**Set-shifting task** data were processed using event-related beamforming software developed in-house. Continuous MEG data were filtered from 1-50Hz and epoched from -100 to +800ms (stimulus onset=time 0). Non-overlapping, sequential 100ms time windows (75ms to 575ms) were submitted to synthetic aperture magnetometry beamforming with a 4mm grid reconstructed encompassing whole head volume. Results for each subject were normalized into stereotaxic space using SPM8, images contrasted between groups and significantly different regions (p_{uncorr}<0.005) identified.

For both data sets, time courses were reconstructed at locations showing significant between-group differences. These “virtual sensors” for set-shift task were submitted to permutation testing and corrected for multiple comparisons (p_{corr}<0.05) using a single-threshold maximal statistic. The “virtual sensors” for Go/No-Go task were submitted to rank-sum test.

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