The Impact of the invisible
Buunk, Anne Marie

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Cognitive deficits after aneurysmal and angiographically negative subarachnoid hemorrhage: memory, attention, executive functioning, and emotion recognition

Anne M. Buunk
Rob J. M. Groen
Wencke S. Veenstra
Jan D. M. Metzemaekers
Johannes H. van der Hoeven
J. Marc C. van Dijk
Jacoba M. Spikman

1 Department of Neuropsychology, University of Groningen, University Medical Center Groningen, the Netherlands
2 Department of Neurosurgery, University of Groningen, University Medical Center Groningen, the Netherlands
3 Department of Neurology, University of Groningen, University Medical Center Groningen, the Netherlands
4 Department of Neuropsychology, University of Groningen, the Netherlands

Published in Neuropsychology (2016)
Abstract

Objective. Our aim was to investigate cognitive outcome in patients with aneurysmal and angiographically negative subarachnoid hemorrhage (aSAH and anSAH), by comparing them to healthy controls and to each other. Besides investigating cognitive functions as memory and attention, we focused on higher-order prefrontal functions, namely executive functioning (EF) and emotion recognition.

Methods. Patients and healthy controls were assessed with tests measuring memory (15 Words Test, Digit Span), attention and processing speed (Trail Making Test A and B), EF (Zoo Map, Letter Fluency, Dysexecutive Questionnaire) and emotion recognition (Facial Expressions of Emotion Stimuli and Tests). Between-group comparisons of test performances were made.

Results. Patients with aSAH scored significantly lower than healthy controls on measures of memory, processing speed, and attention, but anSAH patients did not. In the higher-order prefrontal functions (EF and emotion recognition), aSAH patients were clearly impaired when compared to healthy controls. However, anSAH patients did not perform significantly better than aSAH patients on the majority of the tests.

Conclusions. In the subacute phase after SAH, cognitive functions, including the higher-order prefrontal functions EF and emotion recognition, were clearly impaired in aSAH patients. Patients with anSAH did not perform better than aSAH patients, which indicates that these functions may also be affected to some extent in anSAH patients. Considering the importance of these higher-order prefrontal functions for daily life functioning, and following the results of our present study, tests that measure emotion recognition and EF should be part of the standard neuropsychological assessment after SAH.
Introduction

Idiopathic aneurysmal subarachnoid hemorrhage (aSAH) is a severe condition, with many patients having an unfavorable neurological and neurocognitive outcome (Egge et al., 2005; Quinn et al., 2014). In approximately 15% of all patients with SAH no structural cause for the hemorrhage can be detected (Boswell, Thorell, Gogela, Lyden, & Surdell, 2013). Such cases of idiopathic SAH are typed as angiographically negative SAH (anSAH). Unlike aSAH, anSAH is regarded a more benign disorder, considering the relatively good recovery and the low number of neurological complications reported (Rinkel et al., 1991; Ruelle, Lasio, Boccardo, Gottlieb, & Severi, 1985). However, previous studies mainly focused on neurological outcomes, but there is some evidence for suboptimal neurocognitive and daily life functioning in the long-term in anSAH patients (Canhao, Ferro, Pinto, Melo, & Campos, 1995; Germano et al., 1998).

In aSAH patients, cognitive deficits are frequently found, with attention, processing speed, memory and executive functioning (EF) as the most often affected domains (Al-Khindi, Macdonald, & Schweizer, 2010; Hutter, Gilsbach, & Kreitschmann, 1994). Furthermore, a wide range of complaints is described, in particular mood disturbances and fatigue (Al-Khindi et al., 2010; Kuttubaev, Barugh, & Mead, 2012; Passier et al., 2010; Passier, Post, et al., 2011; Visser-Meily, Rhebergen, Rinkel, van Zandvoort, & Post, 2009). These sequelae can affect daily life functioning negatively; for instance, reported percentages of patients returning to work are lower than 50 (Passier, Visser-Meily, Rinkel, Lindeman, & Post, 2011; Rinkel & Algra, 2011). Higher-order prefrontal functions like EF and social cognition (SC) are crucial for adapting behavior to complex situations and hence for daily life functioning (Radice-Neumann, Zupan, Babbage, & Willer, 2007; Spikman, Milders, et al., 2013). In other patient groups, for instance patients with traumatic brain injury (TBI), clear relations have been found between EF deficits and impaired daily life functioning (Bottari, Dassa, Rainville, & Dutil, 2009). However, to date the extent to which deficits in EF and SC influence return to pre-SAH activities has not been studied. Moreover, SC has hardly been investigated in patients after (a)SAH. SC refers specifically to the ability to perceive and understand socially relevant information (Adolphs, 2001); a crucial component of SC is the recognition of the facial expression of emotions (Blair, 2003; Bornhofen & McDonald, 2008). Deficits in emotion recognition have been found to be an important predictor of behavioral problems after TBI (Babbage et al., 2011; Bornhofen & McDonald, 2008; Spikman, Milders, et al.,
2013); consequently, this might also be the case in patients with (a)SAH.

Unlike in aSAH, no clear evidence has been found for cognitive impairments after anSAH. Some authors found evidence for slightly lower scores considering divided attention, mental flexibility, memory and fluency (Boerboom, Heijenbrok-Kal, Khajeh, van Kooten, & Ribbers, 2014; Hutter et al., 1994; Sonesson, Saveland, Ljunggren, & Brandt, 1989), but others reported cognitive functions to be in the normal range (Germano et al., 1998; Krajewski et al., 2014). In contrast, persistent complaints have been consistently found in anSAH patients, for instance regarding irritability, depression, fatigue and cognitive functioning (Alfieri et al., 2008; Canhao et al., 1995; Marquardt, Niebauer, Schick, & Lorenz, 2000). Also, return to work percentages range from 15% to 57%, equaling those of aSAH patients (Alfieri, Gazzeri, Pircher, Unterhuber, & Schwarz, 2011; Canhao et al., 1995). Possibly, deficits in higher-order prefrontal functions contribute to negative outcome and persisting complaints after anSAH. However, EF has barely been investigated after anSAH, and, similar to aSAH, to date there are no studies that focused on SC.

Only few studies have evaluated cognitive consequences in both anSAH and aSAH patients but these yielded no consensus regarding the differences in neurocognitive outcome when these two groups were compared to each other. Some authors found that cognitive functioning was impaired to a similar extent in both groups (Hutter et al., 1994; Krajewski et al., 2014), others found a trend towards fewer deficits in anSAH patients (Mukerji et al., 2010), but relatively small subgroups were investigated or patients were compared on a limited range of general cognitive tests. We deem it worthwhile to directly compare cognitive profiles of anSAH patients to those of aSAH patients, which might be helpful in finding explanations for the fact that a part of this group has persistent complaints and problems in daily life functioning.

In addition to the initial impact caused by the hemorrhage, several secondary clinical characteristics are purported to play a role in neurocognitive outcome, such as bleeding pattern on CT (in anSAH) (Alfieri et al., 2011; Canovas, Gil, Jato, de Miquel, & Rubio, 2012), site of the aneurysm (in aSAH) (Hutter, Kreitschmann-Andermahr, & Gilsbach, 2001; Manning, Pierot, & Dufour, 2005; Mayer et al., 2002), treatment modality (surgical clipping or endovascular obliteration of the aneurysm [coiling] in aSAH) (Hutter et al., 2001; Mukerji et al., 2010), and the presence of hydrocephalus (Dombovy, Drew-Cates, & Serdans, 1998; Stienen et al., 2014) or vasospasm (Richardson, 1991). Evidence for the exact roles of these factors is conflicting and their precise relationship with
cognitive outcome is unclear.

The aim of the present study is twofold. First, to investigate to which extent both anSAH and aSAH patients are cognitively impaired, by comparing them to healthy controls and to each other. Because of the high rates of emotional, cognitive, and physical complaints previously found after anSAH, we hypothesize that cognitive outcome is not only impaired in aSAH patients, but also in anSAH patients. Secondly, we focused mainly on deficits in higher-order prefrontal functions, in addition to testing for deficits in memory, attention, and processing speed. Deficits in EF have not been studied extensively in anSAH patients before and deficits in SC have not been studied in patients with SAH at all. Considering behavioral problems after SAH found in previous studies, we expect higher-order prefrontal functions to be impaired in SAH patients. Lastly, the impact of aneurysm location, posthemorrhagic hydrocephalus, vasospasm and treatment modality of the aneurysm (only in aSAH) will be taken into account.

Methods

All nontraumatic SAH patients admitted to the University Medical Center Groningen (UMCG) in the period from 2010 to 2013 were eligible for inclusion in this study. Exclusion criteria were age younger than 18 years, serious comorbidity and insufficient proficiency of the Dutch language. The diagnosis of SAH was established by means of a computed tomography (CT) scan on admission and the presence (aSAH) or absence (anSAH) of a symptomatic intracranial aneurysm or vascular anomaly was evaluated using CT angiography (CTA) and/or digital subtraction angiography (DSA). AnSAH was defined as a CT-confirmed idiopathic SAH with a negative CTA and DSA. Information on demographic data (age, sex), clinical condition at admission (World Federation of Neurological Surgeons; Teasdale et al., 1988), and presence of post-hemorrhagic hydrocephalus was collected. Acute symptomatic hydrocephalus was initially treated with (temporary) external lumbar drainage (ELD) or external ventricular drainage (EVD). If symptomatic hydrocephalus persisted beyond the acute post-hemorrhage stage, external drainage was terminated and definitive internal ventriculoperitoneal (VP) shunting was performed. Patients were assessed with Transcranial Doppler sonography (TCD) exams to evaluate and monitor flow dynamics/vasospasm over time in the first two weeks after bleeding.
Vasospasm were diagnosed using norm values of Ringelstein et al. (1990) with a Lindegaard ratio (Lindegaard, Nornes, Bakke, Sorteberg, & Nakstad, 1989) of greater than 3 as indicative for vasospasm.

Approximately six months post-SAH, patients underwent neuropsychological assessment. Three matched (gender, age, educational level) non-overlapping healthy control groups were created based on material from previous studies in which specific test batteries were used and were recruited by means of an advertisement in a local newspaper. Control participants were excluded if they had histories of head injury or other neurological conditions, psychiatric disorders or substance abuse (information obtained per participant’s report). Approval from the Medical Ethical Committee of the UMCG has been obtained. All participants gave written consent and were treated according to the Declaration of Helsinki.

**Measurement instruments**

**Memory, attention, and processing speed**
The 15 Words Test (15WT), a Dutch version of the Rey Auditory Verbal Learning Test (Deelman, Brouwer, van Zomeren, & Saan, 1980), measures verbal memory. The score is the total words recalled in 5 trials, with a maximum of 75 and 15 for Immediate Recall (IR) and Delayed Recall (DR) respectively. Working memory was assessed with the Digit Span of the Wechsler Adult Intelligence Scale (WAIS) (Stinissen, Willems, Coetsier, & Hulsman, 1970). The score is the total strings repeated, with a maximum of 30.

The Trail Making Test (TMT) (Reitan & Wolfson, 1985) measures psychomotor speed and attention. The scores are the time (in seconds) needed to complete part A (psychomotor speed) and part B (switching attention).

**Executive functioning**
The Zoo Map test measures planning ability (Wilson, Alderman, Burgess, Emslie, & Evans, 1996) and has a maximum score of 16. The Dutch version of the Controlled Oral Word Association Test (Benton & Hamsher, 1976), Letter Fluency, measures verbal fluency and divergent thinking. The total score is the number of accurately produced words in three minutes.

The Dysexecutive Questionnaire, including a version to be filled in by a close other (DEX and DEX-Proxy; Wilson et al., 1996), measures executive
impairments in daily life. This questionnaire has a maximum score of 80, whereby a total score above 27 points indicates dysexecutive problems (Spikman, Milders, et al., 2013).

**Emotion recognition**

Recognition of facial expressions of emotion was investigated with the Facial Expressions of Emotion Stimuli and Tests (FEEST; Young, Perrett, Calder, Sprengelmeyer, & Ekman, 2002). Sixty faces expressing the primary emotions Fear, Happiness, Disgust, Anger, Sadness or Surprise are presented to the participant with a maximum score of 60.

**Statistical analysis**

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0. Educational level was recorded with the Dutch classification system (Verhage, 1964), ranging from 1 (no primary school) to 7 (university), which was dichotomized as low (1-4) and high (5-7). Test performances were examined in contrast to normative data as used in clinical practice and performances below the tenth percentile or a cut-off score in case of the FEEST and Zoo Map, were considered to be impaired (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Neuropsychological test scores were checked for normal distribution by using quantile-quantile (Q-Q) plots, nonparametric alternatives were applied in case of not-normally distributed scores. Mean scores (M) on the different tests were compared between anSAH, aSAH and healthy controls, using Mann-Whitney U and independent t-tests. Effect sizes (Cohen's d) were calculated for all between-group comparisons. The overall alpha level (p) was set at 0.05 and in case of multiple comparisons, Bonferroni Holm corrections were used (Holm, 1979).

**Results**

In a 2-year period, 203 SAH patients were admitted to the UMCG. Of these patients, 15 died in the hospital. Of the remaining 188 patients, 69 patients were approached but declined to participate or did not participate because their clinical outcomes did not allow for a detailed neuropsychological evaluation. Therefore, 119 SAH patients (90 aSAH, 29 anSAH) were included in this study. Demographic and SAH characteristics are shown in Table 1.
### Table 1. Characteristics of SAH patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>aSAH (n = 90)</th>
<th>anSAH (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, number of women</td>
<td>62 (68.9%)</td>
<td>15 (51.7%)</td>
</tr>
<tr>
<td>Mean age at time of the SAH, years</td>
<td>53.1</td>
<td>53.6</td>
</tr>
<tr>
<td>Time since SAH, months, mean (range)</td>
<td>5.2 (3-8)</td>
<td>4.8 (2-12)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (1-4)</td>
<td>34 (37.8%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>High (5-7)</td>
<td>56 (62.2%)</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>WFNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (1-3)</td>
<td>72 (80%)</td>
<td>28 (96.6%)</td>
</tr>
<tr>
<td>High (4-5)</td>
<td>18 (20%)</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELD/EVD</td>
<td>65 (72.2%)</td>
<td>11 (37.9%)</td>
</tr>
<tr>
<td>VP shunt (after ELD/EVD)</td>
<td>17 (18.9%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Vasospasm on TCD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67 (74.4%)</td>
<td>10 (34.5%)</td>
</tr>
<tr>
<td>No</td>
<td>23 (25.6%)</td>
<td>19 (65.5%)</td>
</tr>
<tr>
<td>Treatment aSAH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clipping</td>
<td>22 (24.4%)</td>
<td></td>
</tr>
<tr>
<td>Coiling</td>
<td>66 (73.3%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm location (^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>69 (76.7%)</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>21 (23.3%)</td>
<td></td>
</tr>
</tbody>
</table>

**Note.** SAH, subarachnoid hemorrhage; aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons; ELD, external lumbar drainage; EVD, external ventricular drainage; VP shunt, ventriculoperitoneal shunt; TCD, Transcranial Doppler sonography. \(^a\) Aneurysm localization, divided in anterior circulation (aneurysms originating from the anterior cerebral artery, anterior communicating artery, middle cerebral artery or internal carotid artery) and posterior circulation (aneurysms originating from the posterior communicating artery or vertebrobasilar artery system).
Comparison of aSAH patients, anSAH patients and healthy controls

Table 2 shows demographic data for the control groups 1 (15WT), 2 (Zoo Map, TMT, Digit Span and Letter Fluency) and 3 (FEST). These three control groups were each separately compared with the patient group; statistical testing revealed no significant differences between each of the control groups and patients (all $p$s > 0.05).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group 1 $^a$ ($n = 97$)</th>
<th>Control Group 2 $^b$ ($n = 77$)</th>
<th>Control Group 3 $^c$ ($n = 101$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, number of women</td>
<td>55 (56.7%)</td>
<td>48 (62.3%)</td>
<td>67 (67.3%)</td>
</tr>
<tr>
<td>Mean age, years, mean (SD)</td>
<td>49.6 (18.16)</td>
<td>56.1 (10.47)</td>
<td>52.2 (9.40)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (1-4)</td>
<td>43 (44.3%)</td>
<td>13 (16.9%)</td>
<td>25 (24.8%)</td>
</tr>
<tr>
<td>High (5-7)</td>
<td>54 (55.7%)</td>
<td>64 (83.1%)</td>
<td>76 (75.2%)</td>
</tr>
</tbody>
</table>


Memory, attention, speed and executive functions

Table 3 shows results of Mann-Whitney tests or $t$-tests for differences in mean scores on tests for memory, speed/attention and EF of both patient groups and healthy controls as well as the percentages of patients who were impaired on these tests. Patients with aSAH scored significantly lower than healthy controls on all measures, effect sizes were moderate to large (Cohen’s $d$ between 0.42 and 0.90). Patients with anSAH did not score significantly lower than healthy controls, effect sizes were low (Cohen’s $d$ < 0.50). However, anSAH patients neither differed significantly from aSAH patients on most measures, except for the TMT-B and Letter Fluency. Effect sizes of the differences between anSAH and aSAH patients were low to moderate (Cohen’s $d$ between 0.22 and 0.56).
Table 3. Performance on neuropsychological tests and comparisons between aSAH patients, anSAH patients and healthy controls

<table>
<thead>
<tr>
<th>Measure</th>
<th>aSAH % impaired</th>
<th>anSAH % impaired</th>
<th>Controls % impaired</th>
<th>aSAH M(SD)</th>
<th>anSAH M(SD)</th>
<th>Controls M(SD)</th>
<th>aSAH vs controls T/U</th>
<th>P</th>
<th>d*</th>
<th>T/U</th>
<th>P</th>
<th>d*</th>
<th>T/U</th>
<th>P</th>
<th>d*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15WT IR</td>
<td>54.5*</td>
<td>41.4</td>
<td>27.8</td>
<td>38.28 (10.29)</td>
<td>41.69 (12.19)</td>
<td>43.36 (10.89)</td>
<td>-3.25</td>
<td>0.001**</td>
<td>0.47</td>
<td>-0.71</td>
<td>0.48</td>
<td>0.15</td>
<td>1.48</td>
<td>0.14</td>
<td>0.32</td>
</tr>
<tr>
<td>15WT DR</td>
<td>13.6</td>
<td>3.4</td>
<td>9.3</td>
<td>7.74 (2.98)</td>
<td>8.79 (2.76)</td>
<td>9.25 (3.26)</td>
<td>-3.27</td>
<td>0.001**</td>
<td>0.49</td>
<td>-0.68</td>
<td>0.49</td>
<td>0.15</td>
<td>1.68</td>
<td>0.10</td>
<td>0.36</td>
</tr>
<tr>
<td>Digit Span</td>
<td>25*</td>
<td>7.4</td>
<td>5.2</td>
<td>12.85 (2.96)</td>
<td>14.33 (3.39)</td>
<td>14.58 (2.73)</td>
<td>-3.89</td>
<td>0.000**</td>
<td>0.61</td>
<td>-0.39</td>
<td>0.70</td>
<td>0.09</td>
<td>2.20</td>
<td>0.03</td>
<td>0.49</td>
</tr>
<tr>
<td>Attention, speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-A</td>
<td>16.3*</td>
<td>3.4</td>
<td>5.2</td>
<td>40 (16.26)</td>
<td>32.07 (13.57)</td>
<td>34.14 (11.21)</td>
<td>2581</td>
<td>0.02**</td>
<td>0.42</td>
<td>933</td>
<td>0.19</td>
<td>0.18</td>
<td>822</td>
<td>0.006</td>
<td>0.51</td>
</tr>
<tr>
<td>TMT-B</td>
<td>16.5</td>
<td>3.4</td>
<td>6.5</td>
<td>98.91 (53.20)</td>
<td>72.59 (49.32)</td>
<td>76.71 (35.12)</td>
<td>2401.5</td>
<td>0.003**</td>
<td>0.49</td>
<td>929.5</td>
<td>0.19</td>
<td>0.11</td>
<td>753.5</td>
<td>0.002**</td>
<td>0.51</td>
</tr>
<tr>
<td>Executive Functions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoo Map</td>
<td>41.4*</td>
<td>31</td>
<td>4</td>
<td>6.55 (6.02)</td>
<td>7.86 (6.26)</td>
<td>9.83 (5.18)</td>
<td>-3.70</td>
<td>0.000**</td>
<td>0.58</td>
<td>-1.64</td>
<td>0.10</td>
<td>0.36</td>
<td>1.01</td>
<td>0.32</td>
<td>0.22</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>21.5*</td>
<td>7.7</td>
<td>6.3</td>
<td>30.19 (10.70)</td>
<td>36.07 (10.21)</td>
<td>39.57 (10.17)</td>
<td>-5.36</td>
<td>0.000**</td>
<td>0.90</td>
<td>-1.53</td>
<td>0.13</td>
<td>0.35</td>
<td>2.58</td>
<td>0.01**</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Note. Mann-Whitney tests were used to compare results of the Trail Making Test (TMT). aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; t, statistic of independent t-test; U, statistic of Mann-Whitney test; 15WT IR, 15 Words Test Immediate Recall; 15WT DR, 15 Words Test Delayed Recall.

* Cohen’s d, effect size.
** significant difference in percentages impaired between the patient group (anSAH or aSAH) and control group using a χ² test (p < 0.05).
** significant after Bonferroni-Holm corrections.
Dysexecutive problems (DEX-score > 27) were reported by 26.1% of aSAH and 17.2% of anSAH patients, proxy ratings were 19.5% (aSAH) and 13.8% (anSAH). No significant differences were found between DEX total scores of both groups ($t(115) = -1.92, p > 0.05$) but proxies of aSAH patients reported significantly more dysexecutive problems than proxies of anSAH patients ($t(113) = -2.35, p < 0.05$). DEX and DEX-Proxy scores did not differ significantly in the anSAH group ($t(55) = 0.84, p > 0.05$) and the aSAH group ($t(173) = 0.64, p > 0.05$).

**Emotion recognition**

Table 4 shows the results of $t$-tests for differences in means on the total FEEST score and the six subcale scores of both patient groups and healthy controls as well as the percentages of patients with impaired performances. Patients with aSAH had significantly lower total scores as well as lower Anger and Disgust subscale scores compared to healthy controls, with moderate effect sizes (Cohen’s $d > 0.50$). Patients with anSAH did not differ significantly from healthy controls and neither from aSAH patients on any of the measures. Effect sizes were low (Cohen’s $d < 0.50$) for differences between anSAH and aSAH patients and low to moderate (Cohen’s $d$ between 0.09 and 0.71) for differences between anSAH patients and controls.
**Table 4.** Performance on the FEEST and comparisons between aSAH patients, anSAH patients and healthy controls.

<table>
<thead>
<tr>
<th>Measure</th>
<th>aSAH</th>
<th>anSAH</th>
<th>Controls</th>
<th>aSAH</th>
<th>anSAH</th>
<th>Controls</th>
<th>aSAH vs control</th>
<th>anSAH vs control</th>
<th>anSAH vs aSAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% impaired</td>
<td>% impaired</td>
<td>% impaired</td>
<td>M(SD)</td>
<td>M(SD)</td>
<td>M(SD)</td>
<td>T</td>
<td>p</td>
<td>d\textsuperscript{a}</td>
</tr>
<tr>
<td>Total</td>
<td>30*</td>
<td>17.2*</td>
<td>5</td>
<td>45.64(6.76)</td>
<td>46.21(6.63)</td>
<td>48.85(3.91)</td>
<td>-3.94</td>
<td>0.000**</td>
<td>0.63</td>
</tr>
<tr>
<td>Anger</td>
<td>6.7</td>
<td>10.3*</td>
<td>1</td>
<td>7.55(2.02)</td>
<td>7.38(1.99)</td>
<td>8.46(1.37)</td>
<td>-3.57</td>
<td>0.000**</td>
<td>0.54</td>
</tr>
<tr>
<td>Disgust</td>
<td>16.7</td>
<td>13.8</td>
<td>11.9</td>
<td>7.13(2.17)</td>
<td>7.72(2.04)</td>
<td>8.29(1.78)</td>
<td>-4.03</td>
<td>0.000**</td>
<td>0.59</td>
</tr>
<tr>
<td>Fear</td>
<td>16.7</td>
<td>20.7</td>
<td>11.9</td>
<td>5.51(2.19)</td>
<td>5.52(2.64)</td>
<td>6.11(2.25)</td>
<td>-1.87</td>
<td>0.06</td>
<td>0.27</td>
</tr>
<tr>
<td>Happiness</td>
<td>1.1</td>
<td>0</td>
<td>1</td>
<td>9.84(0.40)</td>
<td>9.90(0.31)</td>
<td>9.85(0.43)</td>
<td>-0.15</td>
<td>0.89</td>
<td>0.02</td>
</tr>
<tr>
<td>Sadness</td>
<td>25.6*</td>
<td>20.7</td>
<td>11.9</td>
<td>6.69(2.13)</td>
<td>7.03(2.24)</td>
<td>7.19(1.76)</td>
<td>-1.79</td>
<td>0.08</td>
<td>0.26</td>
</tr>
<tr>
<td>Surprise</td>
<td>2.2</td>
<td>3.4</td>
<td>3</td>
<td>8.80(1.34)</td>
<td>8.66(1.32)</td>
<td>8.99(1.23)</td>
<td>-1.03</td>
<td>0.31</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Note:* aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; \( t \) = statistic of independent \( t \) test; FEEST, Facial Expressions of Emotion: Stimuli and Tests.

\textsuperscript{a} Cohen’s \( d \), effect size.

*significant difference in percentages impaired between the patient group (anSAH or aSAH) and control group using a \( \chi^2 \) test \((p < 0.05)\).**significant after Bonferroni-Holm corrections.
Cognitive deficits after aneurysmal and angiographically negative subarachnoid hemorrhage: memory, attention, executive functioning, and emotion recognition

Cognitive performances related to differences in secondary clinical characteristics

*Hydrocephalus*

SAH patients (both anSAH and aSAH) with a VP shunt for hydrocephalus performed significantly worse on the 15WT IR ($t(115) = 3.64, p < 0.05$), 15WT DR ($t(115) = 3.86, p < 0.05$), Zoo Map ($t(114) = 2.22, p < 0.05$), Letter Fluency ($t(110) = 2.50, p < 0.01$), and FEEST total score ($t(116) = 2.24, p < 0.05$) than patients without a VP shunt. DEX proxy scores of patients with a VP shunt were significantly higher than those of patients without a VP shunt ($t(113) = -2.72, p < 0.05$), meaning proxies of patients with a VP shunt reported more executive impairments.

*Vasospasm*

No significant differences between cognitive outcome of SAH patients (both aSAH and anSAH) with and without vasospasm on TCD were found (all $ps > 0.05$).

*Treatment*

Patients after surgical clipping performed significantly worse on the Zoo Map, compared to patients after coiling of the aneurysm ($t(85) = 2.13, p < 0.05$). No significant differences were found between clipped and coiled patients on all other cognitive measures (all $ps > 0.05$).

*Aneurysm location*

No significant differences were found between patients with anterior and posterior aneurysms (all $ps > 0.05$).

**Discussion**

In the present study, we found aSAH patients to be impaired on a broad range of cognitive measures, including higher-order prefrontal functions. Although anSAH patients did not perform significantly worse than healthy controls on these measures, they also did not perform significantly better than aSAH patients, indicating suboptimal functioning. In particular we investigated higher-order prefrontal functions, i.e. social cognition and executive functioning, because of
their important role in functioning in daily life. As far as we know, this is the first study that investigated emotion recognition after aSAH. As such, this also is the first study that reports serious impairment in this domain. Again, although emotion recognition of anSAH patients was not impaired when compared to healthy controls, we found clear indications of a trend towards emotion recognition impairments after anSAH.

In aSAH patients, we found deficits in memory, attention and processing speed, similar to previous studies (Al-Khindi et al., 2010; Rinkel & Algra, 2011). Also, executive deficits after SAH have been found before, but we were the first to demonstrate these deficits using a test (the Zoo Map) which has been found to have high ecological validity, that is having a high predictive value for daily life functioning (Josman et al., 2014; Norris & Tate, 2000). Authors who reported executive deficits post-SAH previously used more standard tests focusing on specific aspects of EF, for instance switching and flexibility (Kreiter et al., 2002; Manning et al., 2005; Martinaud et al., 2009) or investigated only a subgroup of clipped aSAH patients (Uchikawa et al., 2014). In addition, we extended our research by also investigating self- and other-reported executive problems. We found that proxies of aSAH patients reported significantly more dysexecutive problems than proxies of anSAH patients, while the two patient groups did not differ in their self-ratings. Possibly, self-ratings reflect the actual problems of patients less accurately than proxy-ratings in the more severely injured aSAH patients. A discrepancy between proxies’ and patients’ ratings is interpreted as indicative for impaired self-awareness in moderate to severe TBI patients (Spikman, Milders, et al., 2013). Also, in stroke patients, who are similar to SAH patients, the method of discrepancy ratings has been successfully used to rate awareness (Langer & Samuels, 2008; Nurmi Laihosalo & Jehkonen, 2014).

Although scores on cognitive tests of anSAH patients were lower than those of healthy controls, the differences were not significant. At the same time, overall cognitive performance of anSAH patients was not significantly better when compared to aSAH patients. In most cases, the means of anSAH patients were between those of healthy controls and aSAH patients. Moreover, effect sizes of the non-significant differences between anSAH and aSAH patients were moderately large, indicating a trend towards impairment in the anSAH patient group. These findings provide more insight in neurocognitive outcome after (an) SAH; cognitive functions are clearly affected in aSAH patients, and apparently not optimal in anSAH patients. In addition, almost one fifth of the anSAH patients had serious dysexecutive complaints. This profile of mild cognitive deficits with
serious complaints in a part of the patient group bears some resemblance to what is found in patients with mild traumatic brain injury (mTBI) (Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007). Results from fMRI studies suggested that mTBI patients need to use additional resources to keep cognitive functioning at a normal level (Smits et al., 2009), causing mental fatigue and a high rate of (cognitive) complaints (van der Horn, Liemburg, Aleman, Spikman, & Naalt, 2015). Possibly, a similar mechanism might explain the discrepancy between relatively intact cognition and severe subjective complaints and impaired daily life functioning after anSAH.

We were the first to investigate emotion recognition, an important aspect of SC, after SAH and found that this was significantly impaired in aSAH patients. Although we did not find significant differences in emotion recognition between anSAH patients and healthy controls, also no significant differences were found between anSAH and aSAH patients. Moreover, a significantly higher percentage of anSAH patients was impaired (i.e. performance below the tenth percentile) when compared to control subjects. These latter findings combined with moderate to high effect sizes indicate that deficits in emotion recognition can be found after anSAH. Deficits in emotion recognition have been extensively demonstrated in patients who sustained a TBI and for this patient group several authors reported a positive correlation between emotion recognition deficits and the presence of social behavioral changes (Milders, Ietswaart, Crawford, & Currie, 2008; Spikman, Milders, et al., 2013). Consequently, it seems reasonable to assume that emotion recognition is crucial for adequate social functioning after SAH as it is in TBI. This warrants further research on SC after SAH.

It has been stated before that prefrontal brain areas play an important role both in emotion recognition and in social behavior (Adolphs, 2001; Zald & Andreotti, 2010). Hence, it seems likely that impaired emotion recognition in SAH patients is related to structural defects in the prefrontal cortex. However, we found no relation between emotion recognition and the location of the aneurysm (if present) or the method of treatment (if performed). This lack of findings may be related to the fact that SAH is a complex disease, with a high risk of secondary ischemic deficits after the initial bleeding, that can occur in vascular territories remote from the site of the symptomatic aneurysm. As such, aneurysm site is not a predictor for the brain area in which secondary ischemic deficits becomes manifest. Also, choice of treatment depends on several factors, such as initial clinical condition, patient comorbidities, aneurysm size, aneurysm shape, and location of the aneurysm (Fraser et al., 2011; Jaja et al., 2015). Therefore, the
reported differences between clipped and coiled patients have to be interpreted with caution, because the groups may also differ with regard to other factors. In the current study, SAH patients with a VP shunt for hydrocephalus scored significantly lower on measures of memory, EF, and emotion recognition than patients without permanent shunt. Although an association between chronic hydrocephalus and neuropsychological deficits has been suggested by several authors (Stienen et al., 2014, 2015), it remained unclear which cognitive domains are most severely affected.

Some limitations of our study have to be taken into account. First, only those patients who were able to undergo extensive neuropsychological testing were investigated; our results may not be applicable to more severely impaired SAH patients. Secondly, we investigated cognitive functioning in the subacute phase (i.e. around 6 months) after SAH. Although this is generally considered to be a clinically relevant phase to evaluate patients (Zweifel-Zehnder et al., 2015), cognitive functioning might change in the following months. Lastly, due to the relatively small number of anSAH patients, a lack of statistical power could be an explanation for the absence of significant differences in cognitive outcome between anSAH patients on the one hand and aSAH patients and healthy controls on the other hand. Effect sizes of these non-significant results were moderately large, indicating that a larger sample of anSAH patients would possibly have resulted in different findings.

In conclusion, our study shows a high rate of cognitive impairments in aSAH patients, including deficits in higher-order prefrontal functions, that is EF and emotion recognition. Although anSAH patients did not perform significantly worse than healthy controls, also only few significant differences were found when their results were compared to those of aSAH patients. Hence, neurocognitive performance in anSAH patients appears to be affected as well, albeit to a lesser extent. Importantly, we were the first to investigate emotion recognition, and found this to be clearly impaired after aSAH. Again, although anSAH patients did not differ significantly from healthy controls on emotion recognition, almost one-fifth was impaired when compared to norm scores and they did not perform better than aSAH patients. Ergo, this indicates that emotion recognition in anSAH patients is at a suboptimal level.

SC and EF are crucial for daily life functioning as was found in a range of studies in patients with moderate to severe TBI (Hanks, Rapport, Millis, & Deshpande, 1999; Novack, Bush, Meythaler, & Canupp, 2001; Spikman, Boelen, et al., 2013). In these studies, emotion recognition deficits were related
to impaired social relationships and behavioral problems (Radice-Neumann et al., 2007; Spikman, Milders, et al., 2013), and EF deficits were associated with reduced daily functioning. Despite the relevance for daily life functioning, these higher-order prefrontal functions are not assessed routinely after SAH. However, it is likely that suboptimal higher-order prefrontal functioning affects SAH patients’ ability to meet the demands of the environment, resulting in the high amount of emotional, physical and cognitive complaints previously found after anSAH (Marquardt et al., 2000; Sonesson et al., 1989) and impaired daily functioning after aSAH (Vilkki, Juvela, Malmivaara, Siironen, & Hernesniemi, 2012). We strongly recommend for clinical practice to perform a comprehensive neuropsychological assessment post-SAH, and to incorporate measures for EF and SC into the series of tests. Considering the relationship between SC deficits and impaired psychosocial functioning as well as behavioral problems after stroke (Blonder, Pettigrew, & Kryscio, 2012; Bornstein & Poon, 2012) and TBI (Milders et al., 2008; Spikman, Milders, et al., 2013; Ubukata et al., 2014), SC is an important topic which requires further study in SAH patients. Timely detection of specific (social) cognitive deficits helps to decide whether early treatment is necessary and to tailor such treatment to individual needs. This will enhance the chance of successful social and vocational reintegration.
References


Cognitive deficits after aneurysmal and angiographically negative subarachnoid hemorrhage: memory, attention, executive functioning, and emotion recognition

dot.2012.48(Suppl.A).1739723 [doi]


Hutter, B. O., Gilsbach, J. M., & Kreitschmann, I. (1994). Is there a difference in cognitive deficits after aneurysmal subarachnoid haemorrhage and subarachnoid...
Cognitive deficits after aneurysmal and angiographically negative subarachnoid hemorrhage: memory, attention, executive functioning, and emotion recognition


Quinn, A. C., Bhargava, D., Al-Tamimi, Y. Z., Clark, M. J., Ross, S. A., & Tennant, A. (2014). Self-perceived health status following aneurysmal subarachnoid haemorrhage:


Cognitive deficits after aneurysmal and angiographically negative subarachnoid hemorrhage: memory, attention, executive functioning, and emotion recognition

Neurosurgery. https://doi.org/S1878-8750(14)00470-7 [pii]

