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.
1

General introduction and outline
Introducing subarachnoid hemorrhage

A subarachnoid hemorrhage (SAH) is a severe bleeding in the subarachnoid space, between the pia mater and the arachnoid membrane. In the majority of cases, SAH is characterized by the rupture of an intracranial aneurysm, defined as aneurysmal SAH (aSAH). In 15% of the cases of SAH, no structural cause for the hemorrhage can be detected, typed as angiographically negative SAH (anSAH). SAH accounts for only 3-5% of all strokes, but is the type of stroke with the highest morbidity and mortality rates (Feigin, Lawes, Bennett, Barker-Collo, & Parag, 2009). The incidence of SAH in the Netherlands is between 5 and 7 cases per 100,000 per year (Risselada et al., 2011). A SAH still carries a case fatality of approximately 35%, despite the fact that this is reduced during the past thirty years, mostly because new diagnostic techniques and therapeutic interventions have emerged (Rinkel & Algra, 2011). Generally, aSAH is treated by either endovascular treatment (coiling and/or stenting) or microsurgical occlusion (clipping or wrapping) of the aneurysm.

A sudden severe headache is the most distinctive symptom of SAH. Other symptoms are neck stiffness, nausea, photophobia, focal neurological deficits or unconsciousness. Main complications are acute hydrocephalus, rebleeding, and vasospasm, with possible delayed cerebral ischemia (van Gijn, Kerr, & Rinkel, 2007). Acute hydrocephalus is generally treated with an external ventricular drain or external lumbar drain. Hydrocephalus that persists beyond the acute stage, i.e. chronic hydrocephalus, requires cerebrospinal fluid (CSF) shunting.

Emotional, cognitive, and behavioral consequences

SAH has a great impact both on the patient and relatives. Cognitive impairment may occur in up to 83% of cases, with main cognitive domains being affected: memory, attention, and language (Al-Khindi, Macdonald, & Schweizer, 2010; Kapadia, Schweizer, Spears, Cusimano, & Macdonald, 2014). However, most of the studies on post-SAH cognitive functioning have focused on patients after aneurysmal SAH, not after angiographically negative SAH. In general, it is suggested that cognitive deficits can remain over years. Cognitive impairment has been associated with clinical features such as hydrocephalus and delayed cerebral ischemia (Ogden, Mee, & Henning, 1993) and demographic variables
such as high age and low education (Kreiter et al., 2002).

Next to objective cognitive deficits as assessed with neuropsychological tests, SAH patients report a wide range of cognitive complaints, such as forgetfulness or planning problems. Furthermore, behavioral problems are often mentioned after SAH, for example apathy (Marin, Biedrzycki, & Firinciogullari, 1991) and inadequate social behavior (Ogden, Utley, & Mee, 1997; Storey, 1970). These behavioral problems are usually measured with self-report questionnaires, but could possibly also be examined using neuropsychological assessment.

Lastly, mood disorders, sleep disturbances and fatigue are major post-SAH consequences (Kutlubaev, Barugh, & Mead, 2012; Rinkel & Algra, 2011; Schuiling, Rinkel, Walchenbach, & de Weerd, 2005). Reported frequencies of fatigue are high (up to 90%) and the numbers vary depending on the instrument used and timing of testing. Depression and anxiety are common after SAH, with prevalence rates up to 54% (Al-Khindi, MacDonald, & Schweizer, 2010; Boerboom, Heijenbrok-Kal, Khajeh, van Kooten, & Ribbers, 2016; Caeiro, Santos, Ferro, & Figueira, 2011; Hedlund, Zetterling, Ronne-Engstrom, Carlsson, & Ekselius, 2011), and presence of symptoms even in the chronic stage post-SAH (Ackerman et al., 2017; von Vogelsang, Forsberg, Svensson, & Wengstrom, 2015). Additionally, post-traumatic stress disorder (PTSD) has been described in SAH patients, with rates varying between 18% and 34% (Huenges Wajer et al., 2018; Hutter & Kreitschmann-Andermahr, 2014; Hutter, Kreitschmann-Andermahr, & Gilsbach, 2001; Noble et al., 2011; Visser-Meily et al., 2013).

**Functional outcome**

As SAH usually occurs at a relatively young age (mean age of 55 years), post-SAH consequences may influence daily functioning for many years (de Rooij, Linn, van der Plas, Algra, & Rinkel, 2007). Although recovery to functional independence is common, many patients still experience a reduced Quality of Life (QoL) (Hackett & Anderson, 2000; Hop, Rinkel, Algra, & van Gijn, 2001). Furthermore, return to work is seriously affected after SAH; up to two-thirds of all patients are unable to return to their pre-SAH employment (Passier, Visser-Meily, Rinkel, Lindeman, & Post, 2011; Powell, Kitchen, Heslin, & Greenwood, 2004). Also, changes in social participation and leisure activities have been reported (Carter, Buckley, Ferraro, Rordorf, & Ogilvy, 2000; Johansson, Hogberg, &
Bernspang, 2007). Different factors have been related to problems in everyday life functioning, such as cognitive complaints, mood disorders, and behavioral disturbances (Carter et al., 2000; Morris, Wilson, & Dunn, 2004; Ogden et al., 1997; Vilkki, Juvela, Malmivaara, Siironen, & Hernesniemi, 2012).

**Aneurysmal SAH versus angiographically negative SAH**

Traditionally, anSAH has been regarded as a benign entity, considering the good overall neurological outcomes and low risk of rebleeding (Rinkel et al., 1991; Ruelle, Lasio, Boccardo, Gottlieb, & Severi, 1985). More recently, persistent complaints of fatigue, mood disorders, and behavioral problems have been found after anSAH (Alfieri et al., 2008; Canhao, Ferro, Pinto, Melo, & Campos, 1995; Marquardt, Niebauer, Schick, & Lorenz, 2000). Studies on the cognitive consequences of anSAH show conflicting results; some authors reported cognitive functions in the normal range (Germano et al., 1998; Krajewski et al., 2014), others found evidence for cognitive impairment post-anSAH (Boerboom, Heijenbrok-Kal, Khajeh, van Kooten, & Ribbers, 2014; Hutter, Gilsbach, & Kreitschmann, 1994; Sonesson, Saveland, Ljunggren, & Brandt, 1989). Also, two studies revealed problems in the resumption of daily activities after anSAH, comparable to those after aSAH (Alfieri, Gazzeri, Pircher, Unterhuber, & Schwarz, 2011; Canhao et al., 1995).

**Higher-order prefrontal cognitive functions**

Although behavioral disturbances, such as apathy and inadequate social behavior, are frequently reported after SAH, the underlying mechanism is unclear. Over thirty years ago, Brooks (1984) already recognized the need to investigate behavioral consequences of brain injury. He argued that especially behavioral problems negatively affect everyday life functioning and cause stress for families and caregivers. Over the course of years, researchers have shown an increased interest in the assessment and treatment of these behavioral disturbances. Specifically, recent studies have focused on the underlying neuropsychological mechanisms of these problems and concentrated on the objective neuropsychological assessment of social behavioral changes. This
has led to the hypothesis that impairments in so called higher-order prefrontal cognitive functions, executive functions and social cognition, may underlie changes in behavior and social competence.

Executive functions comprise those mental capacities needed to initiate, monitor, and regulate complex, goal-directed behavior (Lezak, 1995). These capacities allow us to adapt to new, unstructured situations. Symptoms of executive dysfunction are for instance impulsivity, impaired abstract thinking, poor decision making, and perseveration (Burgess & Simons, 2005). Social cognition is defined as the ability to understand others’ behavior and react adequately in social situations (Adolphs, 2001; Lieberman, 2007). Different aspects can be distinguished, such as the recognition of facial emotional expressions and understanding someone else’s behavior and intentions. A distinction is often drawn between ‘hot’ social cognition, that is the ability to understand others’ emotional states and to show empathy, and ‘cold’ social cognition, that is thinking about something from another person’s point of view (Blair, 2003). An important aspect of cold social cognition is Theory of Mind (ToM): the ability to understand behavior of others, based on their feelings, beliefs, intentions, and experiences. Deficits in social cognition can manifest themselves in several ways; symptoms are for example inappropriate behavior, an inability to show empathy or diminished interest in others.

The prefrontal cortex, as a part of cortical-subcortical circuits, plays a key role in both executive functions and social cognition, hence the name ‘higher-order prefrontal cognitive functions’. More specifically, the dorsolateral prefrontal cortex is important for executive functions and the orbitofrontal and ventromedial prefrontal cortices are mainly involved in social cognition (Lichter & Cummings, 2001). However, these prefrontal areas are largely overlapping regions, and executive functions and social cognition are not solely located in the frontal areas of the brain (Tekin & Cummings, 2002). Therefore, it is interesting to investigate the relationship between higher-order cognitive functions and focal (frontal) as well as diffuse brain damage.

General aim and outline of this dissertation

The main objective of this thesis is to investigate several neuropsychological consequences of subarachnoid hemorrhage, namely cognitive impairments, behavioral problems, and fatigue, and to define their mutual relationship with
long-term outcome. Specifically, this project set out to examine impairments in higher-order prefrontal cognitive functions, social cognition and executive functions, after SAH. A better characterization of post-SAH consequences and their predictive value leads to a better understanding of the nature of disturbances and consequently, can lead to better treatment methods.

First, a general introduction to the subject is given (Chapter 1). In chapter 2, a study on long-term resumption of leisure and social activities is presented, focusing on the influence of executive complaints and lesion location. Chapter 3 presents a study on two major characteristics of fatigue (mental and physical fatigue) and their relationship with long-term functional outcome after SAH. Chapter 4 comprises a description of the cognitive consequences of SAH and comparisons between aSAH and anSAH, focusing on higher-order prefrontal functions. Subsequently, we present a study on a broad range of aspects of social cognition after aSAH in chapter 5. In this chapter, relationships between behavioral disturbances and focal as well as diffuse brain damage will also be described. The predictive value of cognitive functions for return to work is studied in chapter 6. Chapter 7 is a general discussion of the preceding articles, with final conclusions and implications of our findings.
References


Chapter 1


