Towards a Biopsychosocial Explanation of Headache in Patients with Tumors of the Sellar Region: The Role of Personality, Stress Coping and Pain Catastrophizing

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2 Background

2.1 Headache

Headache in general is one of the most common disorders in the world. The World Health Organization (WHO) documents a one-year prevalence of 56.1% of adults in Europe who experience headache at least once per year in Europe. Up to 3.3% suffer from chronic headache on 15 or more days per months (WHO, 2011). The one-year prevalence of headache for Germany is estimated to be 60.2% with a female preponderance (66.6% in women vs. 53% in men) and a decreasing prevalence with older age (77.7% at age 18 to 29 vs. 34.6% at age 70 and older; Radtke & Neuhauser, 2009).

Many studies suggest that headache comes with a huge societal and individual impact (Stovner & Andrée, 2008). An English cross-sectional general population survey estimates that each year a total of 6540 working days per 1000 workers per year are affected by headache. Of these 1327 days are missed completely and 5213 days are affected adversely by a reduced ability to work (Boardman et al., 2003).

The economic burden of a migraine patient in Western European countries is estimated to a cost of €585 per year, adding up to 27 billion euros per year for the whole of Europe (Stovner & Andrée, 2008). With an average cost of €875, in Germany the total costs for migraine are even higher (Neubauer & Ujlaky, 2002). Only a small percentage of these costs (ca. 10%) are accounted for by direct health care costs for diagnosis and therapy. The vast majority are indirect costs from work absenteeism and reduced effectiveness at work (Berg, 2004).

The personal impact of headache can be equally severe. 32.6% of all headache sufferers report days with the inability or reduced ability to do household work and 19.1% report missed social, family or leisure activities due to headache. 19.5% state that their disability due to headache is at least moderate (Boardman et al., 2003). As a consequence, health-related quality of life (QoL) is significantly reduced in patients with headache compared to healthy controls (Solomon et al., 1994, Lipton et al., 2003).
2.1.1 Definition of headache-related Terms

This thesis describes and analyzes the development of headache in patients with tumors of the sellar region (TSR) in detail. As this is a complex process, it is necessary to define some related terms in advance. Descriptive terms are used according to these definitions throughout this thesis:

In the following, the term occurrence of headache is used to refer to the presence of headache at a given point of time (“Do you have headache?”). Onset of headache means the first occurrence of headache in a patient’s history of headache (“When did you have headache for the first time?”). Headache Location is used to describe the exact placement of pain in the head (“Where in your head do you feel pain?”). Severity of headache refers to the subjective intensity of pain a patient experiences during a headache attack (“How much does your head hurt?”). The term headache intensity is synonymous to headache severity and used in this thesis when referring to previous studies using this term. The number of headache attacks during a specific period of time is called headache frequency (“How many headache attacks did you have?”). Disability due to headache is defined as the extent to which a patient’s day-to-day life is impaired by headache (most often measured by the Migraine Disability Assessment; MIDAS). Impact of headache on day-to-day life is a related concept very similar to disability. In the present thesis, the term is only used to directly refer to the results of the Headache Impact Test (HIT-6). Deterioration and improvement of headache are used to describe the development of an existing headache over time (“Did your headache worsen/get better?”). They can be further specified as to whether they relate to the increase and decrease of headache frequency, headache severity or disability due to headache. Treatment response refers to an improvement of headache that can be attributed to a specific therapeutic intervention. Chronification of headache means the deterioration of an existing headache to the point of changing the diagnosis from episodic to chronic headache (cf. section 2.1.2 for diagnostic criteria). An improvement resulting in the complete resolution of headache is termed remission of headache (“Did your headache resolve?”). Development of headache is used in this thesis to describe the complete process of headache evolution from onset to possible remission.

2.1.2 Classification of Headache Types

The International Headache Society (IHS) undertakes great efforts to distinguish diagnostic criteria for different headache types and publishes a standardized classification system, which is widely in use. The International Classification of Headache Disorders is now in its third edition (ICHD-3), although as yet only published in a beta version (IHS, 2013).
Just like its previous versions the ICHD-3 distinguishes between primary and secondary headache. Headache is primary when it exists on its own without any underlying disease. If headache occurs in close temporal proximity to another disorder known to cause headache, it is classified as secondary, even if it mimics the phenotype of primary headache. The ICHD-3 acknowledges the possibility that a pre-existing primary headache can become chronic or worsened by the emergence of another disease. In these cases, both the primary and secondary headache diagnoses should be made. A third category distinguished by the ICHD-3 comprises painful cranial neuropathies, other facial pains and other headaches. These are of no importance for this thesis and will not be discussed here further. The headache types of relevance are presented in more detail in the following sections.

2.1.2.1 Primary Headache

**Migraine.** Migraine is characterized by recurring attacks of typically unilateral headache of a pulsating quality and moderate to severe intensity. It is frequently aggravated by physical activity and can be accompanied by nausea and photo- or phonophobia. Attacks can last up to 72 hours. If headache attacks appear at least on 15 days per month with features of migraine on at least 8 days for more than three months, the diagnosis of chronic migraine is made. A common subtype of migraine is migraine with aura, in which headache is preceded or accompanied by visual, sensory or other central nervous disturbances. Common symptoms during an aura are the perception of shapes or blind spots in the visual field, numbness or tingling sensations in the face or one side of the body as well as speech disturbances. The aura usually starts gradually and resolves fully during the course of one hour (IHS, 2013). The life-time prevalence of migraine in Europe is estimated to be 17%, with women being affected twice as often as men (women 24% vs. men 12%; Stovner et al., 2007).

**Tension-Type Headache.** Tension-type headache (TTH) is the most common headache type affecting about 50% of the inhabitants of Europe with a slight female preponderance (women 55%, men 46%; Stovner et al., 2007). It is typically bilateral with a pressing or tightening quality and of mild to moderate intensity. Headache can be accompanied by nausea and photo- or phonophobia and is not affected adversely by physical activity. TTH attacks can last between 30 minutes and several days. TTH on one or less days per month is diagnosed as infrequent, on up to 14 days as frequent and on more than 15 days as chronic TTH (IHS, 2013).

**Trigeminal-autonomic Cephalalgias.** Trigeminal-autonomic cephalalgias (TACs) include different headache subtypes which are generally severe, strictly unilateral and located orbitally,
supraorbitally or temporally. All TACs share ipsilateral parasympathetic autonomaous features like conjunctival injection (pinkeye), lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, constriction of the pupils and drooping or swelling of the eyelids. They appear periodically with episodes of recurrent pain separated by remission periods of several months or years.

The TAC subtypes differ in pain duration and frequency. The most common TAC is cluster headache which is characterized by headache attacks of 15 to 180 minutes up to 8 times a day. Shorter headache attacks of up to 30 minutes which appear many times per day are termed paroxysmal hemicrania. TACs can also appear as short, frequently recurring stabs with a duration of 1 to 600 seconds. These are diagnosed as short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) according to the accompanying trigeminal-autonomic symptoms. If remission periods do not occur over the course of one year, TAC is considered to be chronic. Persistent TAC, either continuous or varying in intensity, lasting for more than three months without remission periods is diagnosed as hemicrania continua (IHS, 2013).

TAC is a very rare condition. The estimated lifetime prevalence of cluster headache varies between 56 and 381 in 100,000 inhabitants with men being more often affected than women (Broner & Cohen, 2009). SUNCT, SUNA and hemicranias are only reported in individual cases and there are no reliable estimations of prevalences (Boes & Swanson, 2006).

2.1.2.2 Secondary Headache associated with Tumors of the Sellar Region

Table 1 sums up the diagnostic criteria of those diagnoses, which should be considered if headache occurs in relation to TSR. The study rationale of the present dissertation was planned and diagnostics were carried out in accordance to the second edition of the International Classification of Headache Disorders (ICHD-2; IHS, 2004). It has been updated since to the third edition ICHD-3 (IHS, 2013). Therefore, Table 1 includes a comparison of both versions. Underlying disorders in the sellar region, which are acknowledged as possibly causing headache in both versions, are pituitary apoplexies, space occupation by an intracranial neoplasm (in this case TSR) and pituitary hyper- or hyposcretion\(^1\). Note that in the updated version the diagnosis of headache due to increased intracranial pressure caused by neoplasms (ICHD-2 7.4.1) and headache directly attributed to neoplasms (ICHD-2 7.4.2) have been merged (ICHD-3 7.4.1). Also, the improvement of headache

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\(^1\) Whether or not these conditions are actually able to cause headache in patients with TSR is in part still under discussion (cf. section 2.4.2)
after the resolution of the disorder causing the headache is no longer mandatory for the diagnosis of secondary headache. This is of consequence for the estimation of the prevalence of headache attributed to TSR.

Table 1

Comparison of the diagnostic Criteria for Headache associated with Tumors of the Sellar Region (TSR) from the 2nd and 3rd edition of the International Classification of Headache Disorders (ICHD-2 and ICHD-3)

<table>
<thead>
<tr>
<th>ICHD-2</th>
<th>ICHD-3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6.9 Headache attributed to pituitary apoplexy</strong></td>
<td><strong>6.9 Headache attributed to pituitary apoplexy</strong></td>
</tr>
<tr>
<td>A. Any new headache fulfilling criterion C</td>
<td>A. Any new headache fulfilling criterion C</td>
</tr>
<tr>
<td>B. Acute haemorrhagic pituitary infarction has been diagnosed</td>
<td>B. Acute haemorrhagic pituitary infarction has been diagnosed</td>
</tr>
<tr>
<td>C. Evidence of causation demonstrated by at least two of the following:</td>
<td>C. Evidence of causation demonstrated by at least two of the following:</td>
</tr>
<tr>
<td>1. a) headache has significantly worsened in parallel with other symptoms and/or clinical signs of pituitary apoplexy</td>
<td>1. a) headache has significantly worsened in parallel with other symptoms and/or clinical signs of pituitary apoplexy</td>
</tr>
<tr>
<td>b) headache has significantly improved in parallel with other symptoms and/or clinical signs of improvement of pituitary apoplexy</td>
<td>b) headache has significantly improved in parallel with other symptoms and/or clinical signs of improvement of pituitary apoplexy</td>
</tr>
<tr>
<td>2. either or both of the following:</td>
<td>2. either or both of the following:</td>
</tr>
<tr>
<td>a) headache has significantly worsened in parallel with other symptoms and/or clinical signs of pituitary apoplexy</td>
<td>a) headache has significantly worsened in parallel with other symptoms and/or clinical signs of pituitary apoplexy</td>
</tr>
<tr>
<td>b) headache has significantly improved in parallel with other symptoms and/or clinical signs of improvement of pituitary apoplexy</td>
<td>b) headache has significantly improved in parallel with other symptoms and/or clinical signs of improvement of pituitary apoplexy</td>
</tr>
<tr>
<td>3. headache is severe and of sudden or thunderclap onset</td>
<td>3. headache is severe and of sudden or thunderclap onset</td>
</tr>
<tr>
<td>D. Not better accounted for by another ICHD-3 diagnosis.</td>
<td>D. Not better accounted for by another ICHD-3 diagnosis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>7.4.1 Headache attributed to increased intracranial pressure or hydrocephalus caused by neoplasm:</strong></th>
<th><strong>7.4.1 Headache attributed to intracranial neoplasm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Diffuse non-pulsating headache with at least one of the following characteristics and fulfilling criteria C and D:</td>
<td>A. Headache fulfilling criterion C</td>
</tr>
<tr>
<td>1. associated with nausea and/or vomiting</td>
<td>B. A space-occupying intracranial neoplasm has been demonstrated</td>
</tr>
<tr>
<td>2. worsened by physical activity and/or manoeuvres known to increase intracranial pressure (such as Valsalva manoeuvre, coughing or sneezing)</td>
<td>C. Evidence of causation demonstrated by at least two of the following:</td>
</tr>
<tr>
<td>3. occurring in attack-like episodes</td>
<td>1. headache has developed in temporal relation to development of the neoplasm, or led to its discovery</td>
</tr>
<tr>
<td>B. Space-occupying intracranial neoplasm demonstrated by CT or MRI and causing hydrocephalus</td>
<td>2. either or both of the following:</td>
</tr>
<tr>
<td>C. Headache develops and/or deteriorates in close temporal relation to the hydrocephalus</td>
<td>a) headache has significantly worsened in parallel with worsening of the neoplasm</td>
</tr>
<tr>
<td>D. Headache improves within 7 days after surgical removal or volume-reduction of tumour</td>
<td>b) headache has significantly improved in temporal relation to successful treatment of the neoplasm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>7.4.2 Headache attributed directly to neoplasm</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Headache with at least one of the following characteristics and fulfilling criteria C and D:</td>
<td></td>
</tr>
<tr>
<td>1. progressive</td>
<td></td>
</tr>
<tr>
<td>2. localised</td>
<td></td>
</tr>
<tr>
<td>3. worse in the morning</td>
<td></td>
</tr>
<tr>
<td>4. aggravated by coughing or bending forward</td>
<td></td>
</tr>
<tr>
<td>B. Intracranial neoplasm shown by imaging</td>
<td></td>
</tr>
<tr>
<td>C. Headache develops in temporal (and usually spatial) relation to the neoplasm</td>
<td></td>
</tr>
<tr>
<td>D. Headache resolves within 7 days after surgical removal or volume-reduction of neoplasm or treatment with corticosteroids</td>
<td></td>
</tr>
<tr>
<td>ICHD-2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ICHD-3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>7.4.4 Headache attributed to hypothalamic or pituitary hyper- or hyposecretion</strong></td>
<td></td>
</tr>
<tr>
<td>A. Bilateral, frontotemporal and/or retro-orbital headache fulfilling criteria C and D</td>
<td></td>
</tr>
</tbody>
</table>
| B. At least one of the following:  
1. prolactin, growth hormone (GH) and adrenocorticotropic hormone (ACTH) hypersecretion associated with microadenomas <10mm in diameter  
2. disorder of temperature regulation, abnormal emotional state, altered thirst and appetite and change in level of consciousness associated with hypothalamic tumour  
C. Headache develops during endocrine abnormality  
D. Headache resolves within 3 months after surgical resection or specific and effective medical therapy |
| **7.4.3 Headache attributed to hypothalamic or pituitary hyper- or hyposecretion** |
| A. Any headache fulfilling criterion C  
B. Hypothalamic or pituitary hyper- or hyposecretion (including prolactin, growth hormone (GH) and/or adrenocorticotropic hormone (ACTH) hypersecretion), associated with pituitary adenoma, has been demonstrated  
C. Evidence of causation demonstrated by at least two of the following:  
1. headache has developed in temporal relation to onset of hypothalamic or pituitary hyper- or hyposecretion  
2. either or both of the following:  
   a) headache has significantly worsened in parallel with worsening of the hypothalamic or pituitary hyper- or hyposecretion  
   b) headache has significantly improved in parallel with improvement in the hypothalamic or pituitary hyper- or hyposecretion  
3. headache is associated with at least one of the following:  
   a) disorder of temperature regulation  
   b) abnormal emotional state  
   c) altered thirst and/or appetite  
D. Not better accounted for by another ICHD-3 diagnosis. |

*Note.* <sup>a</sup> adapted from ICHD-2 (IHS, 2004). <sup>b</sup> adapted from ICHD-3 (IHS, 2013). <sup>c</sup> British English spelling is due to direct quotation from the source.

### 2.1.2.3 Diagnostic Methods

It is estimated that only 40% of all patients with migraine and 25% of those with TTH receive a professional diagnosis. The use of the explicit diagnostic criteria formulated in the ICHD-3 is standard in Germany. However, overall only 66% of all European countries make use of them (WHO, 2011).

In most cases the diagnosis of headache will be established by merely asking for headache symptoms according to the diagnostic criteria. For a more standardized approach, self-reporting questionnaires are available. The Headache Impact Test (HIT-6; Kosinski et al., 2003) and the Migraine Disability Assessment (MIDAS; Stewart et al., 2001) are most widely in use for the evaluation of the disability headache imposes on daily life. The Essener Kopfschmerzfragebogen (Essen Headache Inventory, EHI; Fritsche et al., 2007) is a questionnaire checking the diagnostic criteria for migraine, TTH and TAC available for German speaking patients. Still, these inventories are not a standard part of a clinical routine in Germany (WHO, 2011).

In contrast, imaging or other technical or laboratory investigations are employed on a regular basis. It is estimated that 30% of all patients who consult a specialist (e.g. neurologist) due to headache receive X-ray computed tomography (CT), 10% receive magnetic resonance imaging (MRI), 10% a sinus examination, 9% electroencephalography (EEG) and 2% cerebrospinal fluid examination (CSF; WHO, 2011).
2.2 Sellar Region and Pituitary System

For the understanding of TSR and their possible mechanical and endocrinological influences on headache, a basic knowledge of the structure and function of the pituitary is required. For this reason, the following sections provide a short overview of the pituitary system. Section 2.2.1 gives a summary of the pituitary’s anatomy, followed by explanations of the endocrine functions of the anterior pituitary (section 2.2.2) and the posterior pituitary (section 2.2.3). These sections will explain the main regulatory functions of the pituitary hormones. However, hormone secretion is modulated by a multitude of other neuroendocrine factors. These will only be highlighted insofar as they are of relevance to the understanding of TSR.

2.2.1 Anatomy

The pituitary is a small gland located at the base of the brain. It has a diameter of about 0.5 cm and weighs between 0.6 and 0.8 g. It rests in a bony enclosure called the sella turcica. At the top it is separated from the cranial cavity by the sellar diaphragm, a dural fold. Its location is in close proximity to the optic chiasm and the cavernous sinus in the wall of which the internal carotid artery and several cranial nerves pass by.

The pituitary gland consists of three parts. The pituitary stalk, the posterior pituitary (also called neurohypophysis) and the anterior pituitary (adenohypophysis). The stalk is a small tube which pierces the sellar diaphragm and connects the pituitary to the hypothalamus. The axons of hormone producing nerve cells from the hypothalamus run through it into the posterior pituitary. The posterior and anterior pituitary are anatomically different and each part of two separate endocrine systems (cf. sections 2.2.2 and 2.2.3). They also develop independently from each other in the embryo: while the posterior pituitary develops downwards from the diencephalon, the anterior pituitary is formed by parts of the embryonal ectoderm, the Rathke’s pouch.

The anterior pituitary makes up three quarters of the pituitary. It has three parts: the pars distalis, located frontally, the pars tuberalis, close to the pituitary stalk and the pars intermedia, a narrow region next to the posterior pituitary which can only be found in embryos. Hormone producing cells are located predominantly in the pars distalis. According to the specific kind of hormone excreted

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2 Section 2.2 contains basic medical knowledge, which can be looked up in any endocrinological textbook. In accordance with the conjoint position paper on good scientific practice published by several German university and faculty associations (AFT et al., 2012), this section does not provide literature sources. The interested reader can consult (Petersenn, 2019) for in depth information on these topics.
by the cells, they are categorized as somatotropic, mammotrophic, gonadotrophic, thyreotropic and
corticotropic cells. The anterior pituitary is supplied by a small blood vessel system which is directly
connected to the blood vessel system of the hypothalamus. Via these hypothalamo-hypophysial
portal vessels it receives regulatory hormones from the endocrine cells of the hypothalamus.

The posterior pituitary is much smaller than the anterior pituitary. It consists of axon ends from the
hypothalamus which have synapse-like connections to a capillary system.

2.2.2 Endocrine Function of the Anterior Pituitary

The anterior pituitary receives hormones from the hypothalamus via the portal vessels, which
either increase (releasing hormones) or decrease (inhibiting hormones) hormonal secretion of the
anterior pituitary. Blood circulation transports the pituitary hormones to peripheral organs where
they cause further hormone excretion. Five independent endocrine pathways have been identified.

Adrenocorticotrophic System. The corticotropin-releasing hormone (CRH) is emitted episodically
from the hypothalamus about every two hours. It also underlies a circadian rhythm with the highest
CRH levels emitted in the morning. CRH causes an increased production of adrenocorticotropic
hormone (ACTH) in the anterior pituitary. A rise in ACTH levels can be observed about 15 minutes
after CRH secretion. ACTH itself binds to specific receptors of the adrenal cortex and stimulates the
production of steroids, especially cortisol. Both cortisol and ACTH follow the circadian rhythm of
CRH. The secretion of cortisol again gives negative feedback to the hypothalamus and the pituitary
and thus inhibits further production of CRH and ACTH. Among many other neuroendocrine factors,
CRH secretion is modulated by dopamine.

One function of cortisol in the body is the regulation of the stress response. Its main effect is on the
metabolic system where it stimulates the synthesis of glucose in the liver while inhibiting its
utilisation in the muscles. It also regulates lipid degradation and storage. In the brain cortisol
influences perception, mood and sleep.

Thyrotropic System. Hypothalamic thyrotropin-releasing hormone (TRH) secretion follows a
circadian rhythm with maximum secretion levels around midnight. Also, a pulsatile rhythm with
increased secretion every two to four hours can be observed. TRH stimulates the production of
thyroid-stimulating hormones (TSH) and prolactin in the anterior pituitary. TSH causes an increase
of thyroxin (T3) and triiodothyronin (T4) production in the thyroid gland, which again has an
inhibiting effect on TSH secretion in the pituitary and TRH secretion in the hypothalamus. Clinically
relevant, TSH secretion can also be inhibited by SMS, dopamin or cortisol. TSH as well as T3 and T4 follow the rhythmicity of TRH. Physiologically, T3 and T4 are important regulators of the metabolism. Their release increases the basic metabolic rate and calorie consumption of the body.

**Gonadotropic System.** The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in regular pulses every 90 to 120 minutes. GnRH reaches the anterior pituitary through the portal vessels. It causes an increased production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are the main regulators of gonadal functions in both sexes.

In men, LH stimulates testosterone production in the gonads, which again suppresses GnRH secretion in the hypothalamus. There is no direct inhibiting effect of testosterone on the pituitary. However, its metabolic product estradiol can inhibit LH synthesis directly. FSH stimulates spermatogenesis as well as the production of the hormone inhibin in the male gonads. Inhibit gives negative feedback to the pituitary and thus regulates the production of FSH. FSH is also indirectly affected by testosterone and estradiol through their inhibitory influence on GnRH.

In women, gonadotropic regulation is more complex as LH and FSH secretion vary over the menstrual cycle. FSH stimulates the maturing of ovarian follicles and, in consequence, the production of estrogen in the female gonads. Estrogen stimulates the production of LH in the pituitary by sensitizing the gonadotropic cells for GnRH. The rise of estrogen levels to its peak concentration in the middle of the menstrual cycle and the following surge in LH secretion cause ovulation. LH again stimulates progesterone production in the ovaries, which in low concentrations increases the secretion of FSH and thus causes the midcycle peak in FSH levels. With rising concentrations, progesterone begins to have an indirect inhibitory effect on FSH and LH through its negative feedback to the hypothalamus, though. In consequence, FSH and LH levels fall again as the menstrual cycle continues.

**Somatotropic System.** The production of growth hormone (GH) in the anterior pituitary is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin (SMS) from the hypothalamus. GH is emitted episodically without a regular rhythmicity over the day. Maximum GH secretion is observed at night, when high GHRH secretion and low SMS secretion come together. The amount of daily GH production is age dependent and highest during puberty. Around the age of 60 GH production stops entirely following a decrease in GHRH secretion and an increase in SMS secretion, as well as a reduction of GHRH receptors in the somatotropic cells in the pituitary. GH stimulates the production of insulin like growth factors (IGF) I and II predominantly in
the liver but also in many other organs. Both GH and IGF-I can bind to receptors on almost any tissue and stimulate growth, predominantly of bone and muscle. They also serve metabolic purposes in releasing glucose from the liver for metabolic processing in the muscles.

**Mammotropic System.** Prolactin is produced by the mammotropic cells of the anterior pituitary. It underlies mainly the inhibitory effects of dopamine from the hypothalamus. Since the main function of prolactin is the stimulation of lactation in the mammary glands, its production is increased by feedback from afferent fibers from the areolas, i.e. a nursing child. There are also stimulating effects of estrogen from the ovaries and TRH from the hypothalamus.

Prolactin is emitted episodically around 14 times a day. The prolactin level does not vary with the menstrual cycle but is typically higher at night time. During pregnancy prolactin levels increase significantly due to the stimulating effect of estrogen. This helps preparing the mammary glands for lactation by stimulating the growth of the alveoli. High prolactin levels also inhibit GnRH secretion in the hypothalamus and can thus cause amenorrhea in women and infertility in men.

### 2.2.3 Endocrine Function of the Posterior Pituitary

The posterior pituitary itself does not produce hormones, but stores hormones from the hypothalamus and emits these into the blood circulation. Antidiuretic hormone (ADH) and oxytocin are transported via neuronal axons through the pituitary stalk into the posterior pituitary. Triggered by action potentials, the synapse-like axon endings emit them into the capillary system.

**Antidiuretic Hormone.** The antidiuretic hormone (ADH) is the most important regulatory factor in water homeostasis and diuresis. The production of ADH in the hypothalamus is controlled through feedback via blood pressure and osmolality, meaning the concentration of solutes like sodium chloride, glucose or urea in the blood. Osmolality is measured by specific osmoreceptors in the hypothalamus. While a low osmolality of the blood suppresses ADH secretion, high osmolality stimulates it. Likewise, blood pressure is measured by baroreceptors in the aortic arch and the atrium of the heart. Afferent fibers give feedback via the medulla oblongata to the hypothalamus, causing a decrease in ADH in case of high blood pressure and an increase in case of low blood pressure.

**Oxytocin.** Oxytocin is released from the posterior pituitary and binds on smooth muscle tissue. It is of special importance in the process of giving birth, as the number of oxytocin receptors in the uterus increases right before delivery. A sudden release of huge quantities of oxytocin initiates
contractions of the uterus and thus induces labor. It also affects lactation and facilitates attachment and nurturing between mother and child.

2.3 Tumors of the Sellar Region

The sellar region can be the target of different tumor entities. In the largest surgical series so far, the most frequent TSR was shown to be pituitary adenomas, which constitute 82% of all TSR operated upon. Another 7.5% are craniopharyngeomas and Rathke’s cleft cysts, 3.9% are meningeomas. Other tumorous and non-tumorous lesions include cysts, gliomas, chordomas, hypophysitis, granular cell tumors and carcinomas (Buchfelder et al., 2000).

Owing to the high prevalence of pituitary adenomas in the general population as well as in the present study sample, and in order to touch on their intricate and diverse sequelae, section 2.3.1 covers adenoma subtypes in more detail. Non-adenomatous lesions are introduced briefly in section 2.3.2. Section 2.3.3 describes the special case of pituitary apoplexy.

2.3.1 Pituitary Adenomas

Based on a review of postmortem and radiological findings, the prevalence of pituitary adenomas in the general population is estimated to be around 17% (Ezzat et al., 2004). Most of them are clinically asymptomatic and remain undetected. They can, however, become apparent when hormonal overscretion from the tumor cells leads to symptoms of hormone excess. In addition, the clinical sequelae of hormone deficiency due to compression of the anterior pituitary by the tumor mass can lead to the detection of the tumor. Other symptoms of space-occupying larger tumors include visual disturbances, visual field deficits and – debatably – headache by compression of the surrounding cranial nerves or a stretching of the meninges. If the tumor compresses the pituitary stalk, it prevents dopamine from inhibiting prolactin secretion resulting in secondary hyperprolactinemia (Jockenhövel, 2002) with its associated symptoms. The prevalence of clinically symptomatic pituitary adenomas is about 77 in 100,000 inhabitants (Fernandez et al., 2010).

Pituitary adenomas can be classified according to their size as microadenomas or macroadenomas. Immunohistochemically, they are classified according to the WHO Classification of Tumors of Endocrine Organs, most recently updated to the newest version (Lloyd et al., 2017). Current developments allow an in-depth histological characterization of different adenoma types, a further
explanation of which is beyond the scope of this dissertation3. Clinically, they can be characterized as functioning or non-functioning adenomas, depending on whether they oversecrete an active hormone or not.

**Prolactinomas.** With a prevalence of 30 to 50 in 100,000 inhabitants, prolactinomas constitute around 40% of all pituitary adenomas (Mindermann & Wilson, 1994). They are characterized by prolactin hypersecretion from lactotrophic tumor cells. Microprolactinomas are typically benign, remain intrasellar and most often do not progressively increase in size. Macroprolactinomas are rarer and appear more often in men. They are often invasive tumors with areas of regressive changes. In general, prolactinomas occur significantly more often in women, especially in the third life decade (Casanueva et al., 2006).

Since prolactin suppresses gonadal function by inhibiting GnRH, LH and FSH production, prolactinoma patients present with clinical signs of secondary hypogonadism. The symptoms include infertility, impaired libido, spontaneous milkflow from the breast (galactorrhea) and a disturbed menstrual cycle in women (oligo- or amenorrhea). Also, excessive growth of body hair in women (hirsutism), an increase in breast tissue in men (gynecomastia) and an accelerated risk of osteoporosis are observed (Jockenhövel, 2002).

**GH-secreting Adenomas.** 10% of all pituitary adenomas excrete GH from somatotropic tumor cells. GH-producing tumors are often macroadenomas and nearly always benign. The longtime excess of peripheral GH and subsequently IGF-I induces growth of the acres, soft-tissues and inner organs resulting in the clinical picture of acromegaly. With a prevalence of 5 to 7 in 100.000 inhabitants acromegaly is very rare. The mean age at diagnosis is around 45 years, disease onset is earlier, though. Due to the insidious development of the disease and oftentimes unspecific symptoms at the beginning of GH hypersecretion, there is a long delay in the diagnostic process (Jockenhövel, 2002).

The main presenting symptoms of acromegaly include enlarged hands and feet, coarsened facial features, growth of the jaw and tongue, enlarged interdental spaces, excessive sweating, joint pain and headache (cf. section 2.4.2.2). It can also lead to severe comorbidities like cardiovascular disease, diabetes mellitus, sleep apnea, impaired respiratory function and colonic neoplasms (Adelman et

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3 The matter of immunohistochemical classification of pituitary adenomas is complex and currently evolving. Since it is not of immediate relevance to the present research question, it is not covered in this dissertation. For an overview of recent developments in this field refer to (Lopes, 2017).
al., 2013, Kreitschmann-Andermahr et al., 2016). Compared to the general population, patients with untreated acromegaly have an increased morbidity and mortality (Dekkers et al., 2008). Biochemical control of acromegaly reduces mortality in these patients to the level of the general population (Melmed et al., 2009) However, their QoL can remain impaired for years after successful treatment (Kreitschmann-Andermahr et al., 2017).

**ACTH-secreting Adenomas.** In 5% of all pituitary adenomas, ACTH hypersecretion from corticotropic tumor cells leads to an increase in cortisol production in the adrenal glands and thus to the clinical syndrome of hypercortisolism. Only if hypercortisolism is caused by a pituitary tumor, it is called Cushing’s disease, whereas Cushing’s syndrome is the name given to all other types of hypercortisolism. Cushing’s disease is rare and has a prevalence of 1 to 3 in 100,000 inhabitants. It has a female/male preponderance of 4-6 to 1 and a peak onset at the age of 40 to 50. The underlying tumor is usually a pituitary microadenoma (Jockenhövel, 2002).

Among the most frequent clinical features of Cushing’s disease are weight gain, central obesity, plethora, a disturbed menstrual cycle, muscle weakness, joint pain, hypertension and excessive body hair growth (hirsutism; Newell-Price et al., 2006, Kreitschmann-Andermahr et al., 2015). Psychopathological comorbidities like depression and anxiety are common (Santos et al., 2017). There is also increasing evidence that the subjective impression of cognitive dysfunction reported by patients with Cushing’s disease is reflected in measurable neuropsychological deficits (Forget et al., 2000). This may be related to atrophy of the temporal lobe and especially the hippocampus caused by longtime exposure to cortisol excess (Patil et al., 2007).

Part of the symptomatology of Cushing’s disease can be reversed through a biochemical cure. However, remaining problems like obesity, hypertension and diabetes can persist for years. Also, the average QoL in patients with Cushing’s disease remains impaired for years after successful treatment of the disease (Feelders et al., 2012, Siegel et al., 2016).

**Thyrotropin-secreting Adenomas.** In patients with thyrotropin-secreting adenomas (TSH-omas) the hyperproduction of TSH in the tumor cells of the pituitary leads to an increased release of T3 and T4 in the thyroid gland. The condition is rare and constitutes only 0.5% of all pituitary adenomas. However, the number of diagnosed TSH-omas has tripled in the last decade due to improved immunometric assays facilitating the diagnosis. Currently, the prevalence of TSH-omas is estimated to be 2.8 in 1 million inhabitants. TSH-omas appear at all ages and are equally frequent.
in both sexes. Due to earlier diagnosis the number of discovered microadenomas has increased. Still, the majority (ca. 70%) of all TSH-omas are macroadenomas (Beck-Peccoz et al., 2015).

Patients with TSH-omas present with the clinical picture of secondary hyperthyroidism including symptoms like goiter, weight loss, heat intolerance, nervousness, emotional lability, hand tremor, heart racing and arrhythmias. TSH-producing macroadenomas also frequently become clinically symptomatic by the effects of the increasing tumor mass (visual field disturbance, insufficiency of the anterior pituitary; Jockenhövel, 2002).

**Gonadotropinomas.** With a prevalence of 1 in 100,000 inhabitants, gonadotropinomas constitute only 1% of all adenomas. They are characterized by the secretion of clinically inactive FSH or LH alpha subunits from gonadotropic tumor cells, which normally do not have a significant impact on serum hormone levels. Most often they remain clinically asymptomatic (clinically non-functioning pituitary adenomas) and are discovered only once they progress to macroadenomas. Then, they can cause signs of space occupation like visual field deficits or insufficiency of the anterior pituitary (Jockenhövel, 2002).

**Mixed Adenomas.** There are cases of functioning pituitary adenomas in which the tumor secretes more than one hormone. This is frequent in TSH-omas which have a cosecretion of GH in 17.9%, of prolactin in 10.2% and of LH or FSH in 1.8% of all cases (Beck-Peccoz et al., 2015). Another frequent combination is GH and prolactin, which appears in around 30% of all GH secreting tumors. The resulting clinical picture includes varying combinations of symptoms of hormone excess according to the involved hormone pathways (Jockenhövel, 2002).

**Non-functioning Pituitary Adenomas (NFPAs).** NFPAs are defined by an absence of clinical symptoms indicating hormonal hypersecretion. Their tumor cells either do not express hormones at all (classically termed null cell adenomas) or hormone producing cells are detectable immunhistochemically, yet they do not produce biologically active hormones (silent adenomas). The exact prevalence of NFPAs is difficult to establish since they often go unnoticed until late in the disease when the tumor compresses the surrounding structures. In the clinical setting NFPAs occur with a prevalence of 7 to 9 cases in 100,000 inhabitants. They constitute nearly half of all operated pituitary adenomas (Greenman & Stern, 2009).

NFPAs are slightly more frequent in men and peak at a mean age between 50 and 55 years. The presenting symptoms are usually effects from the tumor mass like visual field deficits, visual disturbances, or hypopituitarism (Greenman & Stern, 2009). With the widespread use of diagnostic
imaging, the frequency of incidentally discovered NFPAs (incidentalomas) has increased, accounting for 26.4% of all operated NFPAs in a recent surgical series (1990-2011; Losa et al., 2013) as compared to 7.9% in an older one from the time period between 1982-2000 (Nomikos et al., 2004).

2.3.2 Non-adenomatous Tumors of the Sellar Region

Non-adenomatous tumors constitute 18% of all TSR (Buchfelder et al., 2000). They include a vast multitude of different neoplastic, vascular, congenital and inflammatory lesions. They differ in histopathology and prognosis, but may be difficult to distinguish from pituitary adenomas and one another based on the clinical picture alone. Table 2 gives a short overview of non-adenomatous sellar lesions including all TSR observed in the present sample.

Table 2

<table>
<thead>
<tr>
<th>cystic epithelial lesions</th>
<th>germ cell tumors</th>
<th>benign tumors</th>
<th>inflammatory diseases</th>
<th>vascular lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>craniopharyngioma</td>
<td>germinoma</td>
<td>meningioma</td>
<td>bacterial abscess</td>
<td>aneurysm</td>
</tr>
<tr>
<td>Rathke’s cleft cyst</td>
<td>teratoma</td>
<td>ependymoma</td>
<td>fungal abscess</td>
<td></td>
</tr>
<tr>
<td>colloid cyst</td>
<td>dysgerminoma</td>
<td>ependymoma</td>
<td>tuberculosis</td>
<td></td>
</tr>
<tr>
<td>lipoma</td>
<td>dermoid cyst</td>
<td></td>
<td>echinococcus cyst</td>
<td></td>
</tr>
<tr>
<td>chordoma</td>
<td>ectopic pinealoma</td>
<td></td>
<td>mucocle</td>
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<tr>
<td>epidermoid cyst</td>
<td>glioma</td>
<td></td>
<td>sarkoidosis</td>
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<tr>
<td>infundibuloma</td>
<td>astrocytoma</td>
<td>metastases</td>
<td>histiozytosis X</td>
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</tr>
<tr>
<td>epidermoid cysts</td>
<td>ependymoma</td>
<td></td>
<td>hypophysitis</td>
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<td></td>
<td>infundibuloma</td>
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<td></td>
<td>oligodendroglioma</td>
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</tbody>
</table>

Note. Adapted from (Jockenhövel, 2002, S. 126).

Due to the close vicinity of anatomic structures in the sellar region, the symptoms of non-adenomatous TSR can be very similar to those of pituitary adenomas. While there is no hormonal hypersecretion from the tumor cells, secondary prolactinemia caused by compression of the pituitary stalk and hypopituitarism due to the compression of the anterior pituitary are frequent. Also, tumor mass effects like visual field deficits, visual disturbances and a diagnostic workup for headache – may it be a symptom of the tumor or not – often lead to tumor discovery. Specific to non-adenomatous TSR are symptoms that point to an involvement of the hypothalamus, such as central obesity in patients with craniopharyngiomas or diabetes insipidus due to insufficient ADH-secretion (Jockenhövel, 2002). Cranial imaging such as MRI or cranial CT usually helps to characterize the different entities prior to therapy.
2.3.3 Pituitary Apoplexy

The acute hemorrhagic or ischemic infarction of a preexisting pituitary adenoma is termed pituitary apoplexy. It is of special importance to the investigation of headache in patients with TSR since the fast expansion of the hemorrhagic or infarcted adenoma tissue leads to sudden onset thunderclap headache, which reliably constitutes the main presenting symptom in this patient group. It is often accompanied by ocular palsy, impaired vision, nausea and vomiting, and, at times, altered consciousness. The latter symptoms can be attributed to hypopituitarism, especially ACTH deficiency, caused by the compression or destruction of the anterior pituitary gland in the process of pituitary apoplexy. In severe cases acute ACTH-deficiency can be life-threatening (Addisonian crisis; Grzywotz et al., 2017).

The incidence of pituitary apoplexy in patients that have been operated upon pituitary adenomas is reported to be between 0.6 and 9.1%. The prevalence in the general population is 6.2 cases in 100,000 inhabitants. Pituitary apoplexy has a male preponderance and can occur at any age, most often in the 5th or 6th life decade (Capatina et al., 2015). Potential risk factors for pituitary apoplexy discussed in the literature include arterial hypertension, anticoagulant medication and diabetes mellitus (Grzywotz et al., 2017).

The distinctive quality of headache in patients with pituitary apoplexy is acknowledged by a separate category in the HIS classification system (ICHD-3 6.9: Headache attributed to pituitary apoplexy; IHS, 2013).

2.3.4 Treatment of Tumors of the Sellar Region

The primary aim in the therapy of TSR is to restitute normal pituitary function and relieve pressure from the tumor mass on the surrounding structures. To this end, neurosurgical removal of the tumor is considered the therapy of first choice in the treatment guidelines for most TSR (Melmed et al., 2009, Beck-Peccoz et al., 2013, Nieman et al., 2015). Only in prolactinomas is medication with dopamine agonists preferred, which inhibit prolactin production and usually lead to tumor shrinkage (Casanueva et al., 2006). In small, clinically asymptomatic NFPAs, mere observation can be considered as a conservative treatment option (Greenman & Stern, 2015).

90% of all pituitary surgeries are carried out through the nose (transsphenoidal surgery). Normally, only large sized tumors which extend beyond the sellar and suprasellar region are accessed via the skull (transcranial surgery). Remission rates vary according to tumor type and professional experience of the neurosurgeon. If the tumor tissue cannot be fully resected or endocrine function
does not completely recover after surgery, additional treatment can be necessary. Treatment options include repeated surgery, medical inhibition of excess hormone production or substitution of hormonal insufficiencies and radiotherapy (Jockenhövel, 2002).

2.4 Headache in Patients with Tumors of the Sellar Region

Previous research on headache in patients with TSR is extensive and partly inconclusive. A systematic review of the existent literature, which covers details that go beyond the scope of this dissertation, was published by our research group in 2013 (Kreitschmann-Andermahr et al., 2013). The following paragraphs give a concise overview of those aspects important to the present study. The interested reader might, however, want to refer to our review or to (Donovan & Welch, 2018).

2.4.1 Prevalence and Clinical Characteristics

Prevalence. The current literature reports a wide range in the prevalences of headache in patients with TSR, ranging from as low as 37.3% (Abe et al., 1998) to up to 70% (Levy et al., 2004). A recent study on a large sample of 278 patients with TSR observed a prevalence for headache of 64% (178 patients) using a general pain questionnaire (GPQ; Dimopoulou et al., 2014). The largest patient group specifically investigated for the prevalence of headache was by Gondim et al. in 2009 (Gondim et al., 2009). The authors reported headache as a major complaint in 44 of 64 patients (68.7%) with pituitary tumors. However, headache was assessed by means of an ad hoc questionnaire, not described in any detail. No information was supplied on the diagnostic criteria used or the time period, in which the headache had occurred. In a further study by Levy et al. (Levy et al., 2004) 63 patients with pituitary disease were interviewed by trained headache specialists prior to treatment on the presence or absence of headache in a time period closely related to the MRI which uncovered the sellar lesion. The authors found a prevalence of 70% (44) patients reporting headache, which compares closely to the results of Gondim and co-workers.

A more conservative diagnostic criterion was applied by Arafah et al. (Arafah et al., 2000). They questioned patients whether they had experienced new onset headache occurring at least twice a week with the need of analgesic medication for pain relief in the 5 years before the diagnosis of a pituitary adenoma. Using this criterion, the authors found a prevalence of 51% headache (25 of 49 patients) in their study group. Probably the best estimation of headache prevalence in pituitary adenoma patients so far has been provided by Schankin et al. (Schankin et al., 2012). By means of a standardized questionnaire, they identified 24 of 61 patients with headache attributed to pituitary adenoma (39.3%). Schankin and co-workers defined this as a) the presence of headache in the three
months prior to surgery, b) the absence of medication overuse and c) the post-operative amelioration of headache by at least 50% with respect to frequency and severity.

A significantly higher prevalence of headache is generally observed in the patient subgroup suffering from pituitary apoplexy, which seems to nearly always result in acute headache. Dubuisson et al., for example, report a prevalence of 91.6% (22 of 24 patients) for headache in patients with pituitary apoplexy (Dubuisson et al., 2007).

**Headache Types.** Patients with TSR can present with all different types of headache. Levy analyzed headache types according to the IHS criteria in 84 patients and found the most frequent headache types to be chronic migraine (39 patients, 46.4%), episodic migraine (25 patients, 29.7%) and primary stabbing headache (23 patients, 27.4%). The rarer headache types included SUNCT (4 patients, 4.8%), cluster headache (3 patients, 3.6%) and hemicrania continua (1 patient, 1.2%). Levy also described a subgroup of 6 patients (7.1%) with a mixture of migraine symptoms (throbbling, nausea, photo- and phonophobia) and cranial autonomic symptoms (lacrimation, ptosis). These headache presentations could not be classified according to the IHS criteria and Levy suspected them to be a unique secondary headache type associated with TSR (Levy et al., 2005).

Other studies, which do not follow the IHS criteria, describe equally diverse headache presentations. Shankin observed 11 of 24 patients with TTH-like headache (45.8%), 7 with migraine-like headache (29.2%), 3 with both TTH and migrainous symptoms (12.5%) and 1 with TAC-like headache (4.2%). Two patients could not be classified (8.3%; Schankin et al., 2012).

Although apparently scarce, the occurrence of SUNCT and SUNA in conjunction with TSR has been repeatedly described in case studies (Chitsantikul & Becker, 2013). Also, one case of hypnic headache – which is a dull pain which develops during sleep and thus wakes the patient – has been published (Garza & Oas, 2009).

Apart from the actual differentiation of headache types, several studies report on the perceived quality of headache. While the majority of Gondim’s patients described their pain as throbbing (24 of 44 patients, 54.5%), only then followed by dull (7 patients, 15.9%), pressing (7 patients, 15.9%), sharp (5 patients, 11.4%) or burning (1 patient, 2.3%; Gondim et al., 2009), Abe observed mostly “head heaviness” in his patients (11 of 19 patients, 57.9%). To a lesser extent also pulsating (6 patients, 31.6%) and dull pain (2 patients, 10.5%) was experienced by the patients (Abe et al., 1998, Gondim et al., 2009).
As with headache frequency, also the quality of the headache experienced in association with pituitary apoplexy is unique. It is consistently described as a severe, sudden onset thunderclap headache which can be accompanied by nausea, vomiting, visual field disturbances, oculomotor palsy or an altered state of consciousness (Dodick & Wijdicks, 1998, Kuzma & Goodman, 1999, Dubuisson et al., 2007, Garza & Kirsch, 2007).

**Headache Location.** With regard to the laterality of the headache no clear pattern arises in patients with TSR. Headache can occur on either side of the head, on alternate sides or each time on the same side, always on both sides at once or sometimes one-sided and sometimes both-sided (Levy et al., 2005). Levy et al. described unilateral headache to be most common (60 of 84 patients, 71.4%), however, other studies (Abe et al., 1998, Gondim et al., 2009) found bilateral headache to be more frequent (e.g. Abe: 89.5% bilaterality, 17 of 19 patients).

Also, a clear connection between tumor location and headache location could not be confirmed so far. Only Chitsantikul et al. reported 5 consistent cases of SUNCT headache strictly ipsilateral to the side of the tumor (Chitsantikul & Becker, 2013). Levy et al. in turn described headache ipsilateral to cavernous sinus invasion in only 10 of 18 patients (55.6%). And while frontal headache would be suspected as the natural result of the frontal location of the TSR, it seems to occur in no more than 65% of the patients (Levy et al., 2005, Gondim et al., 2009). Actually, Abe and co-workers observed it in only 4 of 19 patients (21.1%; Abe et al., 1998). Other, less intuitive headache locations are just as frequently reported: Levy et al. identified 66 of 84 patients with orbital or retroorbital headache (78.6%), 26 with headache of the vertex (31.0%), 24 with occipital headache (28.6%) and 19 with parietal headache (22.6%; Levy et al., 2005). Cases in which the whole head is afflicted by headache have been reported as well (8 of 19 patients, 42.1%; Abe et al., 1998).

Most papers on pituitary apoplexy do not give any information on headache location in this clinical entity. Garza et al. reported that headache consistently remained located at the vertex of the head in a case report of one female patient. Randeva et al. noted in a retrospective analysis of medical records that retro-orbital headache was frequent in patients with pituitary apoplexy (Randeva et al., 1999).

**Onset.** Although it is a critical diagnostic criterion, the exact time point of headache onset is reported in surprisingly few studies on headache in TSR. There are two studies that find headache onset to be close to the diagnosis of TSR in the majority of patients: Abe et al. reported a mean time since headache onset of 8.3 months with a range from 2 days to 4 years in 19 patients with TSR and
headache (Abe et al., 1998). In Gondim’s study group 32 of 44 patients (72.7%) had been suffering of headache for at least one year and a further 8 for more than 12 months (18.1%) prior to diagnosis of a TSR (Gondim et al., 2009).

However, Schankin et al. identified several patients who had suffered from headache for a much longer time. The authors reported 24 of 61 patients (41%) with a history of headache of more than 5 years prior to diagnosis. How many of these study patients were classified as having adenoma-attributed headache is unclear though (Schankin et al., 2012).

Headache in conjunction with pituitary apoplexy almost invariably has a sudden and immediate onset at the time of the apoplexy (Dodick & Wijdicks, 1998, Randeva et al., 1999, Garza & Kirsch, 2007).

**Severity of and Disability due to Headache.** In interviews with trained physicians, the vast majority of the 84 patients with TSR in Levy’s study group described their headache as severe (55 patients, 65.5%) or very severe (17 patients, 20.2%). 2 patients (2.3%) even reported excruciating headache. Only 10 patients (11.9%) had moderate and none (0.0%) had mild headache (Levy et al., 2005).

In contrast, using their own questionnaire, Gondim et al. found headache to be mild in 7 of 44 patients with TSR (15.9%). 14 patients reported moderate headache (31.8%), 15 severe (34.1%) and 8 excruciating headache (9.5%; Gondim et al., 2009).

Other studies focused on the extent to which headache impairs daily functioning. Pereira-Neto et al. used the HIT-6 scale to describe the impact of headache on daily life in 25 patients with TSR and found that headache had an intense impact in 14 patients (56%). Impact was substantial in 2 (8%), moderate in 1 (4%) and slight in 8 patients (32%; Pereira-Neto et al., 2010).

One recent study investigated disability due to headache by means of the MIDAS questionnaire and reported it to be relatively low. 72% of 178 patients with TSR and headache perceived no or little disability due to headache (Dimopoulou et al., 2014).

Headache in patients with pituitary apoplexy is consistently described as having maximum intensity (Dodick & Wijdicks, 1998, Randeva et al., 1999, Garza & Kirsch, 2007).

**Frequency and Duration of Pain Attacks.** The frequency of pain attacks seems to be fairly high in patients with TSR. Abe et al. even described continuous pain in 11 of 19 patients (57.9%), while 8
patients (42.1%) had intermittent episodes of headache (Abe et al., 1998). The prevalence of chronic daily headache, defined as headache attacks on more than 15 days per month, was reported unanimously to be around 53% by Levy and Gondim (Levy et al., 2005, Gondim et al., 2009).

In a detailed breakdown of the frequency of headache attacks, Gondim described 5 patients with less than 1 attack per week (11.4%), 5 with 1 per week (11.4%), 6 with 2-3 per week (13.6%) and 5 with more than 3 per week (11.4%). Both, Levy and Gondim, reported a mean duration of headache attacks between 7 and 8 hours with substantial interpersonal differences ranging from 15 seconds to 4 days (Levy et al., 2005, Gondim et al., 2009).

2.4.2 Pathophysiological Explanatory Models

2.4.2.1 Mechanical Aspects

Tumor Size. One of the most intuitive theories explains headache in patients with TSR as a direct consequence of the mechanical pressure exerted by the pituitary or sellar tumor on surrounding pain-sensitive tissues in the blood vessels, the dura mater or the cranial nerves. According to this theory, pituitary macroadenomas or adenomas, which invade into the cavernous sinus or compress the optic chiasm, should be linked to a higher prevalence of headache.

In support of this theory, Gondim et al. found tumor size, optic chiasm compression and cavernous sinus invasion to be related to a higher incidence of headache in a series of 64 patients with TSR (Gondim et al., 2009). This, however, is the only evidence underscoring the influence of mechanical pressure. Several other studies fail to confirm any relationship between tumor size, cavernous sinus invasion, optic chiasm compression and headache (Abe et al., 1998, Arafah et al., 2000, Levy et al., 2004, Mercado et al., 2004, Yu et al., 2017).

Our own analysis of the potential pathophysiological causes of headache in the present study sample found no evidence supporting the theory of a direct mechanical influence, either4. In fact, both, cavernous sinus invasion and compression of the optic chiasm, were even negatively associated with headache, implying that patients with cavernous sinus invasion or optic chiasm compression had less headache than those without. Adenoma size was unrelated to presence of

4 The analysis of pathophysiological causes in this sample is part of the unfinished doctoral thesis of R. Carneiro Scholl. It is already published together with data from the present thesis in Siegel et al. (2017) and will be cited accordingly.
headache. With a sample size of 112 this is the biggest study group of patients with TSR investigated prospectively on this matter so far (Siegel et al., 2017).

**Intrasellar Pressure.** The normal level of intrasellar pressure (ISP) is not exactly known but estimated to not be higher than 10 to 15 mm Hg. In patients with TSR, ISP was found to be generally higher (Kruse et al., 1992). Raised ISP was mainly found in macroadenomas and was highest in tumors with parasellar extension (Lees et al., 1994). A more recent study reported the highest levels of ISP in macroadenomas confined to the sella without destruction of the sellar floor or diaphragma sellae, though (Gondim et al., 2006).

It has been hypothesized that the increase in sellar contents by the tumor mass leads to a raise in ISP and, thus, causes headache. This hypothesis is supported by findings of extremely raised ISP in patients with pituitary apoplexy, which is characterized by a rapid expansion of the pituitary lesion and almost invariably associated with severe headache (Zayour et al., 2004).

In support of this theory, Arafah and coworkers found significantly higher ISP levels in patients with headache than in patients without, irrespective of tumor size and hypopituitarism, in a sample of 49 patients with TSR (Arafah et al., 2000). But again, this finding did not go unchallenged. A correlation study on 25 patients with TSR did not show any significant relation between ISP and impact of headache on daily life as measured by the HIT-6 questionnaire (Pereira-Neto et al., 2010). Due to lack of further research, the role of ISP in the emergence of headache in TSR patients is not yet completely understood.

### 2.4.2.2 Biochemical Aspects of Pituitary Adenomas in the Pathophysiology of Headache

The following pathophysiology section only pertains to the putative contribution of excessive hormone secretion by hormonally active pituitary adenomas to headache development and the possible impact of hypopituitarism caused by space-occupying sellar tumors on headache. Below, the literature on hormone excess and its relation to headache is presented hormone by hormone.

**Prolactin.** Since the publication of a series of 51 patients with TSR (n=7 prolactinomas) in the 1990ies, which described headache to be more frequent (57.1%, n=4) in patients with prolactinomas than in patients with other adenoma entities (Abe et al., 1998), it has been suggested that prolactin hypersecretion could cause headache (Kreitschmann-Andermahr et al., 2013). Menstrual disturbances in women caused by elevated levels of prolactin have been suggested as one possible reason for this phenomenon (Levy, 2011). Based on observations of prolactinoma patients, in whom the administration of dopamine agonists led to a change in headache phenotype,
it has also been suspected that alterations in the dopamine-prolactin axis might play a role (Levy et al., 2003). However, our own analysis of the present sample of 112 patients with TSR could not detect a relation between headache and hyperprolactinemia or hormonal hypersecretion in general (Siegel et al., 2017).

**Growth Hormone (GH).** A causal role of excessive GH in the development of headache has been suspected, based on observations of a high prevalence of headache (between 60% and 70%) in patients with active acromegaly in large-scaled prospective and retrospective studies (Ezzat et al., 1994, Mercado et al., 2004, Siegel et al., 2017). Still, other studies report headache prevalences of only 24.6% (32 of 130 patients; Almalki et al., 2012) or even only 12.5% (1 of 8 patients; Abe et al., 1998) in acromegaly patients. While headache was frequent in patients with acromegaly in the present sample (69%) we did not see a significant difference of headache prevalence in patients with GH-producing pituitary adenomas to other patients with TSR (Siegel et al., 2017).

The impact of GH hypersecretion on headache is not well understood. It has been suggested to be mediated by the changes in bone and tissue caused by GH hypersecretion (Marzocchi et al., 2005). Some evidence, such as the observation that headache is a frequent adverse effect (1119.6 per 100,000 patients; 1.1%) of the treatment of GH-deficient children with recombinant human growth hormone (rhGh), points to a direct endocrine role of GH in causing headache. Also, the treatment of acromegaly with octreotide, a somatostatin analogue (SSA), frequently alleviates headache in patients with acromegaly. As this effect is not dependent on biochemical normalization of the disease, it has been speculated that octreotide suppresses an – as of yet undefined – nociceptive peptide, involved in headache generation in acromegaly (Williams et al., 1987, Popovic et al., 1988).

### 2.4.3 The Effect of Neurosurgery on Headache

While the IHS recommends treatment of the underlying disease to remedy secondary headache (IHS, 2013), headache alone is usually not considered an adequate indication for neurosurgical removal of TSRs. Due to the difficulties to clearly assign headache to pituitary diseases, Evans and Levy issued an explicit statement against neurosurgery on the sole basis of headache in 2008. They demanded sufficient indication other than headache to justify the removal of pituitary lesions (Evans & Levy, 2008).

If neurosurgery is performed for other clinical reasons, the observed effect on headache varies. Several individual case reports described dramatic headache relief after transsphenoidal surgery (Adamo et al., 2008, Valentinis et al., 2009, Chitsantikul & Becker, 2013). The observed
improvement of headache in retrospective reviews of case reports has been as high as 93% in functioning adenomas (Fleseriu et al., 2009). However, headache remission rates after neurosurgery in prospective studies have been largely unconvincing. Levy et al. reported headache alleviation in only 27 of 55 patients undergoing neurosurgery due to pituitary tumors (49%). 8 patients (15%) even experienced a worsening of their headache (Levy et al., 2005).

Only recently, a prospective study on 79 patients operated transsphenoidally on pituitary adenomas observed that of those 40 patients, with at least moderate headache, 70% experienced an improvement in the 6 months after surgery. The mean headache severity as measured by HIT-6 had decreased significantly after surgery in this sample (Wolf et al., 2016). However, a Norwegian retrospective cohort study among 201 patients with pituitary adenomas, revealed an equally high improvement in the rate of headache with time among patients who had not undergone surgery (64% vs. 82% among operated patients, n.s.; Gravdahl et al., 2016).

In the present sample, the treatment effect of neurosurgery on headache was mainly independent of the clinical characteristics of the tumor. Untreated somatotropic insufficiency was associated with an improvement of disability due to headache after surgery. All other investigated variables, including tumor size, cavernous sinus invasion, hormonal deficiencies and hypersecretions, were unrelated to treatment success (Siegel et al., 2017).

Treatment approaches other than surgery for headache in patients with TSR have rarely been discussed. The options include medical therapy with analgesics, physical therapy or psychotherapy. Patients could also be referred to interdisciplinary treatment groups combining all three of these components. But while there is some evidence for the treatment success of interdisciplinary therapy of primary headache (e.g. Scharff & Marcus, 1994), it has never been investigated if it is equally effective in patients with headache who harbor TSR.

2.5 Proposition of a Biopsychosocial Explanatory Model

In contrast to previous attempts to explain headache in patients with TSR based on exclusively biological models, this dissertation suggests a biopsychosocial explanatory model. The contribution of psychological factors is already widely accepted in research on primary headache and the results from studies in patients with migraine, TTH and TACs were exemplary to the generation of hypotheses in this study. Figure 1 depicts the proposed model of this dissertation. It implies that biological, psychological and social factors each contribute individually to the occurrence and
severity of headache before and after treatment. While the model is displayed in full, only the psychological factors are subject of the current dissertation.

With personality, stress coping and pain catastrophizing this model takes into account three of the main psychological domains that have been found to play a role in primary headache. The model does not by any means claim to be complete, but is meant to give a first conceptual framework for exploratory research in this field.

Figure 1
The proposed Biopsychosocial Explanatory Model of Headache in Patients with Tumors of the Sellar Region (TSR).

Note. Factors and pathways in bold print are subject of the present dissertation.

The following paragraphs will explain in detail the psychological factors investigated in the present dissertation and the evidence from research on primary headache that lead to their inclusion into this study. Section 2.6 will then present the hypotheses derived from the conceptual model.
2.5.1 Personality

Definition. Personality is the set of dispositions that defines a person’s individuality. It is the causal force within the person that influences how a person acts, thinks or feels. It comprises those psychological features that seem central to a person and stay invariable over time and contexts. Knowing a person’s personality helps to understand and predict their reaction to different situations (Carver & Scheier, 2004). The defining features of personality are perhaps best summarized in the words of the influential personality psychologist Gordon Allport:

“Personality is the dynamic organization within the individual of those psychophysical systems that determine his characteristic behavior and thought.” (Allport, 1961, p. 28)

Early personality theories usually sorted people into different personality types conveying that personality is discontinuous and a person can either be one type or the other (e.g. either extraverted or introverted). This approach has been widely criticized as simplifying and unable to fully capture a person’s individuality. It is now more common to think of personality traits. This view regards differences between people as quantitative rather than qualitative and assumes that people differ along continuous dimensions (e.g. more extraverted or less extraverted; Carver & Scheier, 2004).

The history of personality research produced a variety of different scientific approaches to identify those personality traits that are able to describe a person best. However, by now a strong consensus has emerged that the basic structure of personality can best be described in five superordinate personality traits. These became known as the “Big Five” personality dimensions (John & Srivastava, 1999).

The Five Factor Personality Model. The Five Factor Personality Model is based on the psycho-lexical approach which assumes that all salient personality characteristics are represented in the natural language. Following that line of reasoning, Allport et al. derived 18,000 words which serve the description of individual differences of persons from an English dictionary (Allport & Odbert, 1936). This extensive list inspired vigorous efforts to sort and categorize these terms in a structured taxonomy. Eventually, various research groups found a replicable structure of five strong factors in factor analyses on self-rating questionnaires containing abridged versions of Allport’s list. This structure was first termed the “Big Five” by Goldman in 1981 and is by now supported by an extensive body of literature (John & Srivastava, 1999).
There is some debate as to how these five personality dimensions should be named. The NEO-Five Factor Inventory (NEO-FFI), which is the most widely used personality questionnaire assessing them, refers to them as *extraversion*, *neuroticism*, *agreeableness*, *conscientiousness* and *openness to experience* (Borkenau & Ostendorf, 2008). The following section will shortly present each of the five dimensions and what is known about their relation to headache.

### 2.5.1.1 The Influence of Personality on Primary Headache

Research on personality in headache patients was heavily influenced by clinical descriptions of a uniform personality in migraineurs. They were often described to be tense, driven, obsessional and repressing their hostile feelings (Philips, 1976, Schmidt et al., 1986). Psychoanalysts hypothesized that this personality profile leads headache patients to convert unresolved inner conflicts into pain to maintain emotional equilibrium (Naylor et al., 2017). Early research in this field has been criticized for focusing on selective samples (Silberstein et al., 1995) as well as for relying solely on subjective clinical judgement and thus being biased by the researcher’s expectations (Schmidt et al., 1986). The emergence of the “Big Five” personality model allowed an empirical reassessment of the role of personality in the development of headache.

**Neuroticism.** Neuroticism is characterized by emotional instability and an inclination towards negative feelings (Borkenau & Ostendorf, 2008). It has consistently been linked to headache in a vast number of studies (Huber, 2003). While it has been criticized that early research on that matter did not entirely meet methodological standards (Naylor et al., 2017), the crucial role of neuroticism in the development of headache has by now been repeatedly confirmed in methodologically sound studies. For instance, a representative Norwegian population-based study demonstrated higher neuroticism scores in 317 patients with chronic TTH as compared to the general population (Aaseth et al., 2011). Breslau et al. could prove that even when controlled for sex, history of depression and anxiety disorders, neuroticism scores remain elevated in patients with a history of migraine (Breslau & Andreski, 1995). They also demonstrated in a prospective approach that the baseline neuroticism score could predict the first incidence of migraine during a 5 year follow-up period (Breslau et al., 1996). Similar to the hypothesis of the present work, Ishii showed that neuroticism was a significant predictor for the occurrence of migraine in a logistic regression model (Ishii et al., 2012).

**Extraversion.** Extraversion describes the tendency of a person to be outgoing, social and enjoying company (Borkenau & Ostendorf, 2008). It has been proposed to be a protective personality trait that allows patients to better adjust to pain and reduce pain intensity and pain related psychological distress (Connor-Smith & Flachsbart, 2007). While there are some studies describing a positive
impact of extraversion on pain coping in general (Ramirez-Maestre & Esteve, 2013), there is little
evidence for a protective effect of extraversion in the development of headache. Ishii et al. found
introversion, as the counterpart of extraversion, to be a predictor for migraine with aura in a small
subsample (n=24), but not for migraine without aura or migraine in general (Ishii et al., 2012). Also,
several other studies failed to find any relation between extraversion and headache (Kentle, 1989,
Breslau & Andreski, 1995, Schmidt et al., 2011).

**Conscientiousness.** Conscientiousness characterizes a person as determined, disciplined and
thorough and, in its extremes, rigid or obsessive (Borkenau & Ostendorf, 2008). Terms that relate
to excessive conscientiousness can be found almost unanimously in the early clinical descriptions
of personality profiles in migraineurs (cf. Schmidt et al., 1986, for an overview). Thus, the notion of
a perfectionist, rigid, inflexible personality prone to headache inspired a great deal of personality
research in migraine. Surprisingly, there is virtually no empirical evidence substantiating a causal
role of conscientiousness in the development of headache. Neither is it increased in patients with
migraine as compared to non-migraineurs (Magyar et al., 2017), nor can it predict the occurrence
of headache or pain severity in regression models (Schmidt et al., 2011, Ishii et al., 2012, Chan &
Consedine, 2014). Even when including studies that assess conscientiousness under outdated labels
like rigidity, obsessionality or orderliness, no evidence for a central role of conscientiousness for
headache development can be found (Crisp et al., 1977, Blaszczynski, 1984, Schmidt et al., 1986,
Kohler & Kosanic, 1992).

**Agreeableness.** Agreeableness addresses a person’s inclination to be cooperative, friendly,
compassionate and striving for harmony (Borkenau & Ostendorf, 2008). It relates to the
psychoanalytic notion of repressed hostility in headache patients, which has been widely suggested
to play a major role in the development of headache (cf. Philips, 1976 and Schmidt et al., 1986 for
an overview). While there are some studies that suggest that repressed hostility is indeed increased
in migraineurs (Henryk-Gutt & Rees, 1972, Nicholson et al., 2003, Bag et al., 2005), agreeableness
itself cannot predict occurrence of headache or pain severity in regression models (Schmidt et al.,

**Openness to Experience.** Openness to experience describes the extent to which a person is willing
to consider new ideas and engage in new activities. It characterizes a person as imaginative,
inquisitive and receptive to unconventional opinions (Borkenau & Ostendorf, 2008). Recently,
openness to experience has been discussed as a protective factor in patients with headache. While
it may not be able to prevent pain per se (Ishii et al., 2012) it may allow headache patients to be
flexible and creative in their reaction to pain and thus reduce the impact of headache on their day-
to-day life. In accordance, it has been found to be a predictor of lower HIT-6 scores in migraineurs
(Chan & Consedine, 2014) and less pain severity in patients with orofacial pain (Schmidt et al.,
2011). Also, patients with migraine and higher openness to experience have a lower risk for
developing concurrent depression (Magyar et al., 2017).

2.5.2 Stress Coping

Definition. While its historical origins lie in the psychoanalytic investigations of defense
mechanisms, research on coping as it is understood today is based on the transactional theory of
stress response formulated by Lazarus (Folkman & Moskowitz, 2004). His original definition is
largely agreed upon until today:

“From a process standpoint, coping is defined as ongoing cognitive and behavioral efforts to
manage specific external and/or internal demands that are appraised as taxing or exceeding the
resources of the person. The definition can be simplified […] by saying merely that coping consists
of cognitive and behavioral efforts to manage psychological stress.” (Lazarus, 1993, p. 237)

The transactional theory suggests that stress arises from the interaction between a person with
their motivational goals and beliefs and the contingencies of their environment. Persons confronted
with a potentially harmful stimulus engage in two processes of appraisal. During primary appraisal
a person evaluates whether something significant to their well-being is happening. In secondary
appraisal they judge if any actions can be taken to improve the situation. If primary and secondary
appraisal result in the notion that the demands of the situation exceed personal resources, stress
of three different kinds can be experienced: harm, which arises from an already experienced
damage; threat, which is the anticipation of harm; and challenge which signifies the potential of
gain or mastery. A person will then choose a strategy deemed appropriate to overcoming the taxing
situation and act upon it, which is called stress coping. Afterwards, the situation is reappraised.
Thus, stress coping is understood as an adaptive process, reconciling a person’s preferences with
the environmental contingencies (Lazarus & Folkman, 1987).

Coping Strategies. Since coping comprises all available options of behavioral, emotional or
cognitive responses to stress there is a vast multitude of coping strategies that can be identified
and studied. In an ambitious effort to collect all coping strategies ever investigated by different
study groups and assessment tools, Skinner and her colleagues compiled a list of over 400 different
Many important strategies are problem solving, avoidance, support seeking, distraction, direct action, aggression and self-blame (Skinner et al., 2003). Many attempts to identify core categories of coping have been made, yet a consensus is still lacking. The distinction between problem-focused and emotion-focused coping, originally suggested by Lazarus and Folkman, which categorizes coping strategies by their function, is historically important. While problem-focused coping manages the situation through action or decision-making, emotion-focused coping regulates the emotional response to stress (Lazarus & Folkman, 1984). These categories have been universally acknowledged and widely researched; however, they have never been unchallenged. Alternatively, Roth and Cohen suggested to distinguish approach strategies from avoidance strategies contingent on the orientation of coping activities towards or away from the stressor (Roth & Cohen, 1986). Other proposed distinctions include, among many others, behavioral vs. cognitive coping, social vs. solitary coping (both Latack & Havlovic, 1992) and effortful vs. involuntary coping (Compas et al., 1997).

However, the simple dichotomy of these category models appears insufficient to fully encompass the wide scope of coping strategies observed. The main reservation has been that they are not conceptually clear, mutually exclusive or exhaustive, resulting in difficulty appointing single coping strategies to one category or the other. Also, the multitude of different category systems applied impedes comparison and aggregation of results from different studies in this field of research (Skinner et al., 2003).

In view of this heterogeneous literature, Skinner et al. set out to merge the different systems into a comprehensive category model able to comprise all the different coping strategies. To that end they reviewed 100 assessment tools for coping and the way they classified coping strategies into higher order categories. From them they derived 12 core categories which have been separately proven to be unidimensional and homogenous in confirmatory factor analyses for the development of the reviewed coping measures. In a top-down approach, they then organized these core categories according to their adaptive functions into three sets of four categories. Following the theory that coping is an adaptive process realigning an individual under stress with the environment, the model proposes that each coping strategy helps in this process by either a) coordinating the person’s actions with the contingencies of the environment or b) coordinating the person’s reliance on others with the available social resources or c) coordinating the person’s preferences with the available options (Skinner et al., 2003).
Figure 2
Coping Core Categories and their adaptive Functions

Note. Adapted from (Skinner et al., 2003, p. 245).

*aCoping strategies investigated in the present thesis, but not mentioned by exact name in the original figure, were added to the respective categories according to their adaptive function
The resulting model is highly useful and by now widely referenced. It allows identifying related coping strategies and thus facilitates a structured review of the literature. The full model is displayed in Figure 2.

**Adaptive and maladaptive Coping.** It has been argued from the beginning of coping research that the function of a coping strategy should be distinguished from its outcome (Lazarus, 1993). It is possible that a seemingly functional strategy fails to achieve the desired effect. For instance, an attempt to suppress emotions might result in an emotional outburst. Vice versa, given the right circumstances, the most unpopular coping strategies can be appropriate. Exposed, for example, to an uncontrollable stressor, giving up can be the best way to conserve resources. (Skinner et al., 2003) Whether the chosen coping strategy can be called adaptive is thus dependent on the particular person using it, the specific situation in which it is used, the outcome measure (e.g. health, QoL or instant stress relief) and on whether short-term or long-term effects are considered (Lazarus, 1993).

Thus, most researchers in the field agree, that it is impossible to identify coping strategies that are universally dysfunctional or unhealthy. However, although possibly selectively adaptive, the prolonged and rigid use of derogatory (e.g. self-blame or negative thinking), isolating (e.g. withdrawal or opposition) or involuntary negative coping strategies (e.g. helplessness, panic or confusion) can bring about vulnerabilities such as the loss of self-efficacy or interpersonal hostility and come with a greater risk to health (Skinner et al., 2003). It is thus a worthwhile research question (and one objective of the present dissertation) to investigate the effects of specific coping strategies on different life situations and illnesses.

**2.5.2.1 The Influence of Stress Coping on Primary Headache**

Stress is one of the most common triggers of headache attacks. 71-84% of patients with migraine and 82-97% of patients with TTH report stress as a precipitating factor (Martin & MacLeod, 2009). The ability to cope with stressful events is thus an important intrapersonal mediating factor frequently found to have an influence on headache. The following paragraphs give an overview of those coping strategies most consistently found to affect headache. Positive reframing and humor are included although the literature on their influence on headache is inconclusive, since the preliminary data analysis of the present study revealed them to be related to headache in our investigated group of patients. Studies using the BriefCOPE questionnaire are especially relevant to this thesis and highlighted in the following sections, since the BriefCOPE was used in the present study, too. The questionnaire is described in detail in section 3.2.5.
**Denial.** Denial as a coping strategy for stress comprises refusing to believe something stressful happens or persisting that the stressful event is not real. According to Skinner’s category model (Skinner et al., 2003), denial belongs in the core category of escape and thus serves the purpose of exiting an environment that supposedly cannot be influenced directly. Related terms which have been investigated frequently are ‘cognitive avoidance’ and ‘wishful thinking’. Denial as a coping strategy in headache patients would be in line with the psychoanalytic notion, that headache sufferers might ignore inner stress and instead convert it to pain.

Previous research found denial to be a common coping strategy in patients with primary headache. In a sample of patients with epicrania fugax\(^5\) (paroxysmal pain moving across the head) Lopez-Lopez et al. observed significantly higher values of denial than in controls (Lopez-Lopez et al., 2017). Confronted with cognitive stressors in a laboratory setting, patients with migraine displayed more wishful thinking than healthy controls (Hassinger et al., 1999).

Also, denial seems to play a role in chronification of headache by influencing pain appraisal and headache intensity. Marlowe et al. investigated the effect of coping with stressful events during headache attacks on the development of the pain attack and found avoidance to be associated with an increase in headache intensity following the event (Marlowe, 1998). During a pain attack patients with chronic headache who tended to deny present life problems engaged more frequently in headache related thoughts, which in turn correlated with headache intensity, duration and quality (Demjen & Bakal, 1986).

Some studies point to an effect of denial on treatment response to medication and the risk for comorbidities. Significantly higher avoidance (measured by the combined denial and behavioral disengagement subscales of the BriefCOPE) was observed in patients non-respondent to headache medication than in respondent patients (Lucas et al., 2007) and in migraine patients with comorbid fibromyalgia as compared to migraine patients without this comorbidity (de Tommaso et al., 2014).

**Behavioral Disengagement.** Behavioral disengagement means the avoidance of stress to the point of completely giving up all attempts to deal with a stressful situation. Depending on whether disengagement is seen as a conscious choice to avoid harmful influences or resigned passivity

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\(^5\) Epicrania fugax is a rare headache type defined by paroxysmal pain moving across the head. While this sample might not be as representative as a migraine or TTH sample, it is the only sample of headache patients in which the use of coping strategies is compared to controls by means of the BriefCOPE questionnaire.
acknowledging the limit of one’s own actions, it could be assigned either to the escape or helplessness core category of Skinner’s category model.

Stress avoidance is usually perceived as a helpful coping strategy in the management of primary headache. Clinical guidelines as well as popular health websites advise headache patients to identify and avoid possible headache triggers, especially stress which is known to be a trigger for the majority of all headache patients (Schulman & Silberstein, 1992).

And indeed, there is some evidence on the effectiveness of stress avoidance in the prevention of headache. For example, Blau et al. succeeded in reducing headache attacks in a sample of migraine patients by 50% in 82.6% of the participants by advising them to avoid possible headache triggers including stress (Blau & Thavapalan, 1988). Concordantly, Chan et al. found behavioral disengagement as a stress coping strategy to be a significant predictor of a lower impact of migraine on daily life in a logistic regression model (Chan & Consedine, 2014).

However, in recent years the expedience of stress avoidance has been increasingly questioned. It has been criticized that the avoidance of stressful events might lead to a restricted lifestyle and thus be stressful in itself or lead to reduced self-efficacy (Martin & MacLeod, 2009). Martin et al. hypothesized that it is the repeated short exposure to stress resulting from the ongoing attempts to avoid stress that actually perpetuates stress sensitivity. Accordingly, they found that short exposure to stress increased headache and longer (but not maximal) exposure reduced headache (Martin et al., 2007). In a randomized controlled trial of different coping strategies they found trigger avoidance to be similarly effective as no intervention and inferior to active coping strategies in reducing headache (Martin et al., 2014). The authors thus argued against the reliance on stress avoidance for the prevention of headache attacks (Martin, 2010).

Also, several other authors have pointed out negative effects of behavioral disengagement. It seems to be associated with a higher risk of comorbidities and insufficient response to medical treatment. Radat et al. found behavioral disengagement to be higher in migraine patients with depressive and anxious symptoms compared to patients without. Behavioral disengagement was a significant predictor for the occurrence of anxiety in these patients (Radat et al., 2008). Increased behavioral disengagement has also been observed in migraine patients with comorbid fibromyalgia (de Tommaso et al., 2014). Patients non-responsive to medication obtained significantly higher avoidance scores (denial and behavioral disengagement combined) than respondent patients (Lucas et al., 2007).
Self-Blame. Self-blame describes the tendency to criticize oneself as a reaction to stressful situations. According to Skinner it is a strategy of submission in which a person dismisses his preferences in the face of seemingly insurmountable obstacles (Skinner et al., 2003). Other words for self-blame are self-criticism or sometimes internalizing.

While there is little evidence on the influence of self-blame on the development of headache in adults, it is an established risk factor in adolescents. In a large population-based sample of children and adolescents internalizing (e.g. feeling guilty) was a significant predictor of primary headache disorders including migraine, TTH and not-classifiable headache (Kröner-Herwig & Gassmann, 2012). Also, children suffering from weekly headache tended to be more self-blaming than controls when dealing with goal frustration (Massey et al., 2009).

Adult migraine patients engaged more in self-criticizing thoughts than healthy controls in response to a cognitive stressor, i.e. an arithmetic task (Hassinger et al., 1999). However, patients with epicrania fugax did not display more self-blame than controls (Lopez-Lopez et al., 2017) and, surprisingly, one study found self-blame to be a predictor for a lower risk of migraine in adults (Chan & Consedine, 2014).

Still, a self-blaming coping style constitutes one of the main characteristics of depression, which in turn is frequently associated with headache (Vaccarino et al., 2008). Whether this could be due to a causal link between self-criticism and headache is as yet insufficiently investigated.

Substance Use. Substance use as a coping strategy refers to the consumption of alcohol or other drugs for stress relief. According to Skinner’s model it belongs to the core category of escape and thus serves the purpose of leaving a noncontingent environment (Skinner et al., 2003).

Alcohol, as the most frequently used legal drug, is commonly expected to relieve stress and is often used for that purpose (Kuntsche et al., 2006). It is also a known trigger for headache. About 30% of patients with migraine and 50% of all patients with cluster headache report alcohol as a trigger of headache attacks. Since the effect is well-known, these patients tend to abstain from alcohol to prevent pain attacks, thus their overall alcohol consumption is reduced compared to the general population (Dueland, 2015). Concordantly, in the sample of patients with epicrania fugax, substance use as a coping strategy was not more frequent than in controls (Lopez-Lopez et al., 2017).
Even in patients without a history of migraine or TAC substance use can induce headache. This is acknowledged in a specific category of the ICHD-3 (8.1 Headache attributed to use of or exposure to a substance), which among diverse other drugs mentions alcohol as a potential cause of headache. A particular case concerns analgesics, which are taken to relief headache (i.e. pain coping) but can themselves induce chronic headaches when taken excessively (ICHD-3 8.2 Medication-overuse headache; IHS, 2013).

There are not many studies specifically asking for substance use as a means of stress coping in patients with headache. Chan et al., however, found it to be a significant predictor of headache impact and disability due to headache in migraineurs (Chan & Consedine, 2014).

**Humor.** Humor is a rather complex coping strategy. The corresponding items of the BriefCOPE (“I've been making jokes about it.”, “I've been making fun of the situation”) cover a variety of different humorous stress-relieving techniques that might even fall into different core categories of coping.

In their influential work on the psychological aspects of humor, Martin et al. differentiated between four independent types of humor, which have varying influence on well-being. While *affiliative humor* means telling jokes to amuse others and facilitate friendship, *self-enhancing humor* is the tendency to find amusing aspects in the face of stressful situations. Both are seen as benign kinds of humor and supposed to have positive impact on health and well-being. In contrast, *aggressive humor* means the use of sarcasm and derision to create fun at the expense of others. *Self-defeating humor* involves ingratiating oneself to others by self-disparaging remarks. These injurious types of humor are expected to have deleterious effects on the self. And indeed, Martin et al. found the benign types of humor to be correlated to less anxiety and depression and better self-esteem and psychological well-being. Self-defeating humor in turn had a negative influence on all of the above (Martin et al., 2003). It can, thus, be seen either as a strategy of accommodation or of support seeking (Skinner et al., 2003).

There is a multitude of possible health benefits of humor discussed in literature. These range from improved immunity, altered pain sensitivity and lower blood pressure to reduced self-reported illness symptoms and longevity. However, findings in this research area vary greatly and do not altogether back the beneficial effects of humor. This is certainly in part due to the missing differentiation between humor types (cf. Martin, 2001, for an overview).

With regard to headache, to date only one study observed a positive influence of humor on pain intensity. In an Indian study, 20 patients with hypertension and headache received humor therapy
during which they were stimulated to laugh by humorous videos. Pain ratings in these patients improved significantly after humor therapy and were significantly lower than in controls, who did not receive additional therapy of any kind (Awaludin et al., 2018). However, none of the studies using the BriefCOPE to investigate coping strategies in headache patients report an increased use of humor as a coping strategy (Lopez-Lopez et al., 2017) or a significant effect of humor on headache impact, disability due to headache (Chan & Consedine, 2014) or treatment response (Lucas et al., 2007).

**Positive Reframing.** Positive reframing means the effort to change one’s perspective by looking for something good in any stressful situation. It is a strategy of accommodation and thus involves the adjustment of preferences according to the available options. Similar terms include cognitive restructuring, positive thinking or positive reappraisal (Skinner et al., 2003).

Per se, the coping strategy of positive reframing is not more common in patients with headache than in controls (Massey et al., 2009, Lopez-Lopez et al., 2017). Neither is it a significant predictor of headache impact or disability due to headache in migraineurs (Chan & Consedine, 2014).

However, cognitive restructuring plays an important role in the therapy of headache. It is one of the main components of cognitive-behavioral therapy (CBT), which has been proven to effectively reduce migraine (Fritsche et al., 2013), TTH (Rosen, 2012) and (in combination with pharmacotherapy) chronic daily headache (Lipchik & Nash, 2002). While standard CBT mixes cognitive reconstructuring techniques and behavioral activation, an older study by Holroyd et al. suggests that cognitive reappraisal is effective on its own. In a small sample of 10 patients with TTH and 3 or more headache attacks per week, all patients achieved a reduction of headache activity of at least 43% through a cognitive training aimed at the reframing of stress-related thoughts. The cognitive training was significantly more effective than biofeedback therapy or no therapy at all (Holroyd et al., 1977).

The ability to positively reframe thoughts about stressful situations also seems to mediate the effectiveness of medical treatment. In a large epidemiological study, positive reinterpretation (including positive reframing, distraction and humor from the BriefCope categories) was a significant predictor of treatment response to medication in migraineurs (Lucas et al., 2007).
2.5.3 Pain Catastrophizing

Definition. Pain catastrophizing refers to a person’s cognitive response to impending pain. It describes the tendency to magnify the pain’s significance and react with worry and fear. Sullivan gives the following definition:

“Catastrophizing has been broadly conceived as an exaggerated negative “mental set” brought to bear during actual or anticipated pain experience.” (Sullivan et al., 2001, p. 53)

According to Sullivan et al. pain catastrophizing includes three independent dimensions which can be reliably replicated in factor analyses: magnification, which refers to the overestimation of the threat posed by pain, rumination, which refers to the inability to divert attention away from pain and helplessness, which means the belief that one is unable to deal with pain. In the terms of Lazarus’s transactional theory, magnification and rumination can be understood as primary appraisal processes and helplessness as a secondary appraisal process (Sullivan et al., 2001). The three dimensions are represented in the scales of the widely used catastrophizing questionnaire, the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995).

Interaction between Cognition and Pain. Pain catastrophizing has been consistently linked to a heightened pain experience and increased disability caused by pain in various diseases including, among many others, rheumatoid arthritis and low-back pain (Sullivan et al., 2001). However, how exactly pain catastrophizing is able to influence pain perception is still a matter of discussion.

It has been suggested, that the appraisal of pain as a direct threat would lead to an attentional shift towards the threatening information, i.e. the pain. This might cause an increased sensitivity towards unpleasant sensations and might lead a person to interpret ambiguous sensations as painful (Sullivan et al., 2001). In support of this notion, persons with high levels of pain catastrophizing exhibited increased attentional interference in a discrimination task when threatened with a painful stimulus (Crombez et al., 1998).

Pain catastrophizing might even be directly linked to physiological pain reactions. Bandura could prove, that persons confident in their ability to tolerate pain, emitted endogenous opiates and were able to endure more extreme pain stimuli (Bandura et al., 1987). It may thus be hypothesized, that the catastrophizing belief to be helplessly subjected to pain would prevent endogenous opiate release.
Pain catastrophizing also influences pain behavior. Persons scoring high in pain catastrophizing showed more intense expressions of pain (e.g. verbal or facial expressions of distress, distorted posture or activity avoidance) and, in consequence, received more instrumental support from their caregivers (Keefe et al., 2003) than study participants who did not use this coping strategy extensively. They were also more likely to utilize health care services and consume analgesics (Sullivan et al., 2001). It can be speculated, that in this context pain catastrophizing could be selectively adaptive. The exaggerated expression of pain could solicit assistance or empathetic responses in health care professionals or social contacts. But in the long run, it could inadvertently heighten and prolong the pain experience (Sullivan et al., 2000).

2.5.3.1 The Influence of Pain Catastrophizing on Primary Headache

Pain catastrophizing is an important influencing factor in primary headache. Compared to healthy controls, migraine patients reported significantly more catastrophizing when dealing with painful events (Hassinger et al., 1999). Although it only accounted for a small amount of explained variance, pain catastrophizing was a relevant predictor for the occurrence of weekly headache (Drahovzal et al., 2006).

More importantly though, it influences the way a patient experiences and reacts to an existing headache. Regression analyses repeatedly confirmed that pain catastrophizing is a strong predictor of pain intensity, impact of headache on daily living and disability due to headache (Buenaver et al., 2008, Kröner-Herwig & Maas, 2013) even when controlled for the effects of depression, anxiety and migraine characteristics (Holroyd et al., 2007). It also had a significant influence on QoL in migraineurs (Holroyd et al., 2007). A study in obese women with migraine suggested that pain catastrophizing increases the risk for depression, anxiety and low self-efficacy (Bond et al., 2015). Pain catastrophizing might even reinforce suicidal thoughts in headache patients as one study found higher pain catastrophizing in headache patients with suicidality than in those without (Rathod et al., 2016).

Pain catastrophizing is supposed to be of relevance in headache treatment. Scientific support of this theory is scarce, though. In a specifically designed CBT group treatment targeting the reduction of pain catastrophizing thoughts, 50% of the headache patients experienced a clinically relevant reduction of pain. However, overall headache frequency and intensity after treatment were not significantly lower than in a waiting-list control group (Thorn et al., 2007).
2.6 Hypotheses

The present dissertation is meant to expand the view on headache causality in patients with TSR from a purely biological pathophysiological explanation toward a more holistic biopsychosocial explanatory model. Focusing on psychological aspects, its main objective was to explore which influencing factors apart from the underlying disease might affect headache in these patients. Since there are no preceding works, which investigate psychological predictors of headache in patients with TSR, hypotheses for this study were based on the comparable research in the field of primary headache. On the assumption that causal relations between psyche and headache might be similar in primary and secondary headache, three psychological domains, i.e. personality, stress coping and pain catastrophizing, were investigated as possible influencing factors. Confer to section 3.4.1 for information on how these theoretical factors were operationalized in this study.

**Personality.** The five personality factors have all been discussed as influencing factors of primary headache, albeit to varying degrees. Especially, the roles of neuroticism as a personality risk factor and extraversion and openness to experience as protective personality factors are supported by the literature and are expected to play a role in the development of headache in patients with TSR as well. Thus, the following hypothesis 1 is formulated:

1. Personality is a significant predictor of
   a. headache occurrence
   b. disability due to headache

in patients with TSR scheduled for neurosurgery.

The hypothesis will be retained if any of the five investigated personality factors adds significantly to the amount of explained variance in the logistic regression model.

**Stress Coping.** Stress is one of the most common precipitating factors of primary headache and its effect is clearly mediated by a person’s ability to cope with it. Denial, Behavioral Disengagement, Self-Blame and Substance Use have all been found to significantly influence primary headache. In addition, our preliminary correlation analyses suggest that in patients with TSR humor and positive reframing might also play a role. Hypothesis 2 is therefore:
2. Stress Coping is a significant predictor of
   a. headache occurrence
   b. disability due to headache
in patients with TSR scheduled for neurosurgery.

**Pain Catastrophizing.** The literature on pain catastrophizing and primary headache is unanimous in its conclusion, that a negative mental reaction to pain aggravates headache frequency and severity. Pain Catastrophizing is thus expected to play a similarly central role in the prediction of headache in patients with TSR. Accordingly, hypothesis 3 reads:

3. Pain Catastrophizing is a significant predictor of
   a. headache occurrence
   b. disability due to headache
in patients with TSR scheduled for neurosurgery.

Hypothesis 2 and 3 will be investigated in a combined regression model (c.f. section 3.4 for further explanation of that rationale). Only factors, that add to the amount of explained variance of the combined regression model will be accepted as relevant predictors. Individual correlation to headache occurrence and disability due to headache will be noted but not be interpreted as sufficient for the confirmation of hypotheses 2 and 3.

**Effect of Neurosurgery.** The validation of therapeutic procedures was not the main aim of this study. However, due to the prospective study design our dataset contains valuable information on that matter that should not be neglected. The analysis of the treatment effect of neurosurgery on headache in patients with TSR was thus included as a secondary objective and hypothesis 4 is phrased as follows:

4. Neurosurgical tumor removal significantly reduces
   a. headache occurrence
   b. disability due to headache

The hypothesis will be retained if a) the frequency of patients recovering from headache after surgery is significantly higher than the frequency of patients experiencing new headache after
surgery and b) the mean disability due to headache after surgery is significantly lower than before surgery.

**Influence of psychological Factors on Treatment Success.** While in primary headache psychosocial factors, especially stress coping strategies, have been identified as predictors of treatment response, no study has as yet investigated the influence of psychological factors on the treatment effect of neurosurgery in patients with TSR. We hypothesize that the same influencing factors affecting headache before surgery might affect the development of headache after surgery and thus formulate the following hypothesis 5:

5. Change of disability due to headache after surgery is significantly related to
   a. personality
   b. stress coping
   c. pain catastrophizing

The hypothesis will be retained if one of the respective psychosocial variables correlates significantly with change in disability due to headache after surgery.
3 Patients and Methods

The present dissertation is part of an extensive research project on the causes of headache in patients with TSR. Two further dissertations from the same project were planned to focus on clinical and neuropathological aspects of the explanatory model. Therefore, several parameters which are not part of the dissertation presented here have been assessed throughout the study. For reasons of completeness these parameters are briefly described in the study procedure (section 3.1.). The materials section 3.2 will concentrate on those psychometric inventories actually used in this dissertation.

3.1 Study Procedure

The study was carried out in the time between July 2012 and August 2013 in cooperation between the Department of Neurosurgery and the Institute for Neuropathology of the University Hospital Erlangen. A prospective single-center study design was followed. The study was approved by the Ethics Committee of the University of Erlangen-Nuremberg in July 2012 (Re.-No. 57_12 B). The ethics committee was informed of the amendment to the study protocol and stated their approval in February 2013. The study was conducted according to the Declaration of Helsinki. All patients received a detailed patient information leaflet and a personal introduction into the study rationale by a member of the research team and provided written informed consent thereafter. Figure 3 shows an overview of the complete study procedure.

Baseline (t1). Patients were enrolled into the study during their stay in the Neurosurgical Department prior to pituitary surgery (cf. section 3.3 for inclusion criteria and sample description). After consent to participate in the study, a set of questionnaires was presented to them on a handheld computer (PainDetect, software version 4, provided by Pfizer GmbH, Germany, cf. section 3.2.1). This included the Migraine Disability Assessment (MIDAS, cf. section 3.2.2), Essen Headache Inventory (EHI, cf. section 3.2.3), Visual Analogue Scales (VAS), Patients’ Health Questionnaire (PHQ-D) and Nottingham Health Profile (NHP). Additionally, all patients were asked to fill out the NEO-Five Factor Inventory (NEO-FFI, cf. section 3.2.4) in a paper and pencil version.

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6 Unfinished works by R. Carneiro Scholl and H. Engelke
After inclusion of the first 41 patients and the results from an intermediate correlation analysis, which indicated that psychological factors were of high relevance to the explanation of headache in patients with TSR, it was decided to extend the study by introducing two further psychometric paper-pencil inventories. All subsequent patients received the BriefCOPE (cf. section 3.2.5) and the Pain Catastrophizing Scale (PCS, cf. section 3.2.6) in addition. In the following, the data collection with the original questionnaire set will be termed Phase A of the study, while the data collection with the amended questionnaire set will be referred to as Phase B of the study. The extension of the study design during the course of the ongoing study results in reduced sample sizes for all analyses including data from the PCS and BriefCOPE.

Beside the psychometric data, clinical data were obtained from the patients’ case records. All patients had undergone a standardized clinical neurological exam and a neuroendocrinological
laboratory screening on the day of admission to the hospital as part of the normal admission routine. Also, preoperative MRI films were available for all patients. After surgery, operative reports were obtained from the surgeon conducting the procedure and histological diagnosis of the lesion was provided by the Institute of Neuropathology, Friedrich-Alexander-University of Erlangen-Nuremberg. Of this extensive data set, predominantly obtained to identify possible biological predictors of headache, only the reason for a diagnostic MRI and endocrinological and histological diagnoses were of relevance to this dissertation for sample description.

**Follow-up (t2).** All patients were contacted again by mail for a follow-up investigation on an average 7.1 months after surgery. They received a paper-pencil-version of the same questionnaires they had originally answered on the PainDetect handheld-computer.

### 3.2 Materials

#### 3.2.1 PainDetect

PainDetect (PainDetect, software version 4, provided by Pfizer Pharma; Junker et al., 2008) is a screening tool for pain, specifically designed for the daily use in clinical practice. The software comprises a multitude of screening questionnaires, out of which the MIDAS (cf. section 3.2.2) and the EHI (cf. section 3.2.3) were chosen for this dissertation. The software comes pre-installed on a handheld computer. The chosen questionnaires are presented to the patients on a 5.5 cm x 5.5cm screen and can be answered with the help of an electronic pen. The version of the device used in this dissertation is shown in Picture 1. While some of the scales included in the PainDetect software have been cross-validated with paper-pencil versions, this is not the case for the two questionnaires in use. Although the primary goal of PainDetect is to facilitate clinical practice, the software has been of use for headache research as well (Dimopoulou et al., 2014).
3.2.2 Migraine Disability Assessment (MIDAS)

The MIDAS questionnaire was developed by Stewart et al. for the assessment of patients’ headache-related disability (Stewart et al., 2001). In this dissertation the translated German version from painDetect provided by Pfizer was used.

Structure. In the painDetect version of the questionnaire patients are first presented with an entry question, in which they are asked whether they had headache within the last three months. Only upon confirmation, are the remaining questions presented. The questionnaire contains 5 items asking for the number of days within the last three months during which the patients experienced limitations in work, school, housework and social activities due to headache. The number of lost days reported in the 5 items is added up to obtain the MIDAS Score. A MIDAS Score lower than 5 signifies minimal or infrequent disability (MIDAS Grade I), a score between 6 and 10 signifies mild disability (MIDAS Grade II), a score between 11 and 20 signifies moderate disability (MIDAS Grade III) and a MIDAS Score higher than 21 signifies severe disability (MIDAS Grade IV). Two additional items assess the total number of days on which headache was experienced and average pain intensity rated on a visual scale from 0 to 10 (by convention multiplied by 10 for statistical analysis).

An illustrated presentation of “headzones”, on which patients can locate exactly where they experience headache is unique to the PainDetect version of the inventory. Patients are presented with four different views of the head with up to ten zones each (cf. fields 1 to 10 in Figure 4) they could mark as hurting. The results were presented visually to the investigator. Dependent on the areas (cf. fields A to N in Figure 4), in which the patient marks headache zones, headache location
was interpreted as front, back, patient’s right side, patient’s left side or whole head. Cf. Figure 4 for the definition of headache locations used for this dissertation.

**Figure 4**

*Interpretation of Headache Locations in the MIDAS Headzones Module*

<table>
<thead>
<tr>
<th>Headache Location</th>
<th>Definition</th>
<th>Illustration of Headache Zones and Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Front</td>
<td>Headache only in area A</td>
<td><img src="image1" alt="A" /></td>
</tr>
<tr>
<td>Back</td>
<td>Headache only in area B</td>
<td><img src="image2" alt="B" /></td>
</tr>
<tr>
<td>Left side</td>
<td>Headache only in areas C, D and E and at least in area E or a combination of C and D</td>
<td><img src="image3" alt="C D E" /></td>
</tr>
<tr>
<td>Right side</td>
<td>Headache only in areas F, G and H and at least in area H or a combination of F and G</td>
<td><img src="image4" alt="F G H" /></td>
</tr>
<tr>
<td>Whole head</td>
<td>Headache in each one of the areas I, J, K, L, M and N</td>
<td><img src="image5" alt="I J K L M N" /></td>
</tr>
<tr>
<td>Mixed</td>
<td>Headache fitting none of the definitions above</td>
<td><img src="image6" alt="Mixed" /></td>
</tr>
</tbody>
</table>

*Note.* 1-10: headache zones presented to the patient. A-N: areas for the interpretation of headache location by the investigator.

**Validation.** The MIDAS questionnaire has been validated in two population-based samples in the USA and United Kingdom with similar results (Stewart et al., 2001). Both studies report a good test-
retest reliability of $r_{rt}=0.8$ over three weeks for the MIDAS Score. Cronbach’s alpha of 0.73 to 0.76 reflects an acceptable internal consistency. Construct validity has been evaluated by correlation with the results from a daily headache diary. The MIDAS score correlated to the equivalent measure from the diary by $r=0.63$ indicating adequate construct validity. Regarding discriminant validity it has been shown that MIDAS discriminates accurately between migraine patients and controls.

3.2.3 Essen Headache Inventory (EHI)

The EHI was developed by Fritsche et. al in 2007 (Fritsche et al., 2007) as a screening tool for migraine, TTH and TACs based on the ICHD-2 (IHS, 2004). It has been originally published in German language and was used in the version provided on the painDetect handheld device.

**Structure.** Patients are first presented with an entry question confirming that they have headache. If patients negate the entry question the remaining items are not presented. The questionnaire consists of three modules, each focusing on one of the three investigated headache types (migraine, TTH and TAC). Each module starts with a short description of the corresponding headache type and the question of whether and how often per month a patient suffers from this headache type. If the patient confirms the presence of the described headache, the detailed diagnostic criteria for this specific headache diagnosis according to ICHD-II are presented individually as yes/no-items. Additionally, the number of days per month on which headache was present at all and on which pain medication was taken is queried. Based on the patients answers the questionnaire allows the following classifications: Chronic and episodic migraine with or without aura, chronic and episodic TTH, chronic and episodic TAC, medication-induced headache, chronic daily headache, non-classifiable headache and combinations thereof.

**Validation.** The questionnaire was validated in 278 headache patients from a clinical population (Fritsche et al., 2007). For construct validation, the results from the questionnaire were compared to the clinical diagnosis of experienced physicians. Cohen’s Kappa was 0.64 for combined diagnoses and 0.93 for mono diagnoses indicating an adequate construct validity. Repeated use of the questionnaire after four weeks revealed a good retest reliability with $r_{rt}=0.948$.

3.2.4 NEO-Five-Factor-Inventory (NEO-FFI)

The NEO-FFI is a personality questionnaire based on the Five Factor Personality Model presented in section 2.5.1. It is the shorter version of the NEO-PI-R and has originally been published by Costa and McCrae in 1989 (Costa & McCrae, 1989). It has been developed in a factor analytic approach and been revised repeatedly since. The version of the questionnaire used in this dissertation was
the second edition of the German translation by Borkenau and Ostendorf (Borkenau & Ostendorf, 2008).

**Structure.** The questionnaire comprises 60 items that all state specific personality traits (e.g. “I am a very active person”). Patients are instructed to rate whether a statement applies to them. Answers are given on a 5-point Likert scale between I strongly disagree (0) and I strongly agree (4). Statements differ regarding their item orientation. Thus, negatively phrased items need to be reversed for interpretation. The questionnaire measures 5 personality scales with 12 items each: Extraversion, Neuroticism, Agreeableness, Conscientiousness and Openness to Experience.

**Validation.** The questionnaire has been validated in a non-clinical population with N=11724 participants (Borkenau & Ostendorf, 2008). An average internal consistency of Cronbach’s alpha =0.80 (0.72 to 0.87) demonstrates a good reliability of the five scales. Retest-reliability for the scales is equally high. Repetitive testing in a subsample of n=146 participants revealed retest-reliabilities between rt=0.65 and rt=0.81 after two years. Another prospective study found retest-reliabilities between 0.71 and 0.82 in a sample of N=1730 participants after 5 years. Factorial validity is well established. The 5-factor structure has been determined in principal component analysis and has been replicated in various subsample analyses. The five scales have very low intercorrelations (r=0.02 to r=-0.36). Substantial correlations to self-descriptions on corresponding adjective scales (r=0.54 to r=0.80) further stress the good construct validity of the test. Age and gender-specific norms from a German representative quota sample are available.

### 3.2.5 BriefCOPE

The BriefCOPE is a measure of coping strategies and was developed by Carver in 1997 to provide a shorter version of the established COPE (Carver et al., 1989). For the short version, the theoretically conceived and factor analytically confirmed COPE scales were reduced to those items that had high factor loadings and comprehensible wording (Carver, 1997). The German translation by Knoll et al. (Knoll et al., 2005) was used in this dissertation. It is available for free use on the original authors’ web page (Carver, undated).

**Structure.** The BriefCOPE consists of 28 items stating possible coping strategies (e.g. “I've been making jokes about it”). Participants are instructed to rate to which extent these statements apply to their thoughts and behavior in past unpleasant or difficult situations. Responses are given on a 4-point Likert scale between not at all (1) and very much (4). The questionnaire measures 14 scales with two items each: Self-distraction, Active coping, Denial, Substance use, Use of emotional

Validation. The BriefCOPE questionnaire has been validated in a sample of 168 participants recently affected by a hurricane (Carver, 1997), showing acceptable internal consistency of Cronbach’s alpha >0.50 for all scales. The factor structure of the BriefCOPE has been in question, since several international factor analytic studies, including the original validation study in the hurricane sample, resulted in fewer factors. However, a recent validation study for the German version in a heterogeneous sample with N=606 participants performed confirmatory factor analysis on concurring models and found a good model fit for the 14-factor model (RMSEA =0.036, CFI=0.9657), which was superior to that of other models. There is a high intercorrelation between the factors, though (Monzani et al., 2015). Correlation patterns to goal commitment and goal progress were supportive of an adequate construct validity in the same study.

3.2.6 Pain Catastrophizing Scale (PCS)

The PCS was developed by Sullivan in 1995 and measures catastrophizing thoughts and feelings concerning pain (Sullivan et al., 1995). For this dissertation the German version provided by Sullivan was used. It was available for free use on the author’s webpage (Sullivan, undated) at the starting time of this study. It is by now licensed and available via Mapi Research Trust, Lyon, France (Mapi, undated). Permission to use this scale was obtained for this study.

Structure. The questionnaire consists of 13 items stating thoughts and feelings associated with pain (e.g. “I feel I can’t stand it anymore”). Participants are instructed to rate to which degree they experience these when they are in pain. Answers are given on a 5-point Likert scale between not at all (0) and all the time (4). The results are added up for a total score. Also, three subscales Rumination, Magnification and Helplessness are available. The total score ranges from 0 to 52 with higher scores indicating higher pain catastrophizing. A PCS score of 30 corresponds to the 75th percentile in the norm population and reflects clinically relevant pain catastrophizing.

Validation. The validity of the PCS is documented in a multitude of studies. Exemplary, Osman investigated the factor structure, validity and reliability in a 1997 report of three subsequent studies (Osman et al., 1997). Therein, the three-factor structure proposed by the original authors was replicated with moderate factor intercorrelations in a principal component analysis of N=188

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7 A root mean square error of approximation (RMSEA) below 0.06 and a comparative fit index (CFI) above 0.95 indicate a good model fit.
students. It was again confirmed in a confirmatory factor analysis of N=220 students, which revealed a good model fit (CFI=0.97, RMSEA=0.067). Internal consistency was acceptable for the three subscales (Cronbach’s alpha > 0.70) and excellent for the PCS total score (Cronbach’s alpha > 0.90) across all three studies. The substantial correlation of r=0.590 of the PCS total score with a similar questionnaire measuring the same construct (Inventory of Negative Thoughts in Response to Pain) points to a good construct validity. Discriminant validity is supported by significant differences between a clinical pain sample (n=86) and a nonclinical sample (n=86) in the PCS total score and all subscales (all p<0.001). For the interpretation of PCS scores, percentiles from a clinical norm sample of N=851 injured workers are available (Sullivan et al., 1995).

3.3 Sample Description

Recruitment. Considered for study entry were all patients scheduled for first-time surgery of tumors of the sellar and suprasellar region in the Neurosurgical Department of the University Hospital Erlangen. Patients aged below 18 years at time of study entry, with a history of brain injury, known alcohol or substance abuse, acute psychotic illnesses or insufficient German language fluency with inability to understand the study rationale or the questionnaires were excluded. Thus, a total of 167 patients were approached and asked to participate. Of these, 112 patients agreed to take part in the study. 41 patients were enrolled during Phase A of the study, an additional 71 patients during Phase B (cf. Figure 3). After surgery, 68 of the original 112 patients (29 from Phase A, 39 from Phase B) answered to the postal follow-up investigation. This results in a response rate of 60.7%.

Baseline Sample. The baseline sample encompassed 53 male and 59 female patients. They were aged between 18.0 and 84.5 years with a mean of 51.5 years and a standard deviation of 17.1 years. 27 (24.1%) of the investigated patients had received tumor diagnosis through MRI due to serious headache. Other reasons for MRI were visual impairments (n=18, 16.1%), suspected Cushing’s disease (n=13, 11.6%), suspected acromegaly (n=12, 10.7%), reduced libido (n=5, 4.5%) or other (n=29, 25.9%). 8 (7.1%) patients had received tumor diagnosis by chance. 102 patients (91.1%) were operated upon via a transnasal-transphenoidal approach, while in 10 patients (8.9%) a transcranial tumor removal or reduction was performed. All patients were operated upon by the same surgeon (MB). The detailed clinical characteristics of the baseline sample, including frequencies of diagnoses according to postoperative histology, clinical diagnoses, and hormonal abnormalities is given in Table 3. Table 4 summarizes the psychological characteristics of the study group.
**Table 3**

Clinical Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline sample (N=112)</th>
<th>Follow-Up sample (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathological diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>84 (75.0)</td>
<td>48 (70.6)</td>
</tr>
<tr>
<td>Cranioopharyngeoma</td>
<td>2 (1.8)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Meningeoma</td>
<td>6 (5.4)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Rathke’s cleft cyst</td>
<td>6 (5.4)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Colloid cyst</td>
<td>4 (3.6)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Normal pituitary tissue</td>
<td>2 (1.8)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (7.1)</td>
<td>5 (7.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline sample (N=112)</th>
<th>Follow-Up sample (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive pituitary adenoma</td>
<td>40 (35.7)</td>
<td>26 (38.2)</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>11 (9.8)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td>Cushing’s Disease</td>
<td>14 (12.5)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>16 (14.3)</td>
<td>10 (14.7)</td>
</tr>
<tr>
<td>Pituitary Apoplexy</td>
<td>4 (3.6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline sample (N=112)</th>
<th>Follow-Up sample (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unreplaced gonadotrophic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficiency</td>
<td>32 (28.6)</td>
<td>19 (27.9)</td>
</tr>
<tr>
<td>Unreplaced thyreotrophic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficiency</td>
<td>6 (5.4)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Unreplaced corticotrophic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficiency</td>
<td>7 (6.3)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Unreplaced somatotrophic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficiency</td>
<td>21 (18.8)</td>
<td>14 (20.6)</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hormone excess</td>
<td>54 (48.2)</td>
<td>26 (38.2)</td>
</tr>
<tr>
<td>Any hormone deficiency</td>
<td>45 (40.2)</td>
<td>27 (39.7)</td>
</tr>
</tbody>
</table>

* Normal pituitary tissue in patients with clinical diagnosis of central Cushing’s disease. * Others are: epidermoid (n=1), spindle-cell oncozytoma (n=1), metastasis (n=1), hypophysitis (n=1), chordoma (n=1), collagen connective tissue with ossification and calcification (n=1), carcinoma (n=1), metastasis of breast cancer (n=1). * Others are: spindle-cell oncozytoma (n=1), metastasis (n=1), hypophysitis (n=1), chordoma (n=1), carcinoma (n=1).

**Follow-up Sample.** The follow-up sample consisted of 68 patients of which 39 were female and 29 were male. They were aged between 18 and 80 years with a mean age of 55.8 years and a SD of 16.3 years. Time interval since surgery was on average 7.1 months (SD 2.6 months). Of those patients who answered the follow-up questionnaire, 16 (23.5%) had received the MRI that lead to tumor diagnosis due to headache, 10 (14.7%) due to visual impairments, 9 (13.2%) due to suspected acromegaly, 7 (10.3%) due to suspected Cushing’s disease and 1 due to reduced libido (1.5%). 19 patients (27.9%) stated other reasons for the MRI and 6 patients (8.8%) had received tumor diagnosis by chance. 63 patients (92.6%) had received transnasal-transphenoidal surgery and 5
(7.4%) transcranial surgery. Clinical characteristics of the follow-up sample are likewise detailed in Table 3 and psychological characteristics in Table 4.

**Drop-Outs.** Patients who did not take part in the follow-up investigation were on average 7.7 years younger than those of the follow-up sample (mean age 46.9 years, SD 16.6 years, p=0.019). Gender distribution (n=20 (45.5%) male vs. n=24 (54.5%) female), was not significantly different from the follow-up sample ($\chi^2=0.101$, p=0.750). Drop-outs had significantly lower scores on neuroticism and extraversion in the NEO-FFI, but none of the other psychological variables was significantly different to the follow-up sample (cf. Table 4). Patients did not state reasons for exiting the study.

**Table 4**

<table>
<thead>
<tr>
<th>Means and Standard Deviations of the Psychological Characteristics in the Subsamples</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEO-FFI N</td>
</tr>
<tr>
<td>NEO-FFI E</td>
</tr>
<tr>
<td>NEO-FFI O</td>
</tr>
<tr>
<td>NEO-FFI C</td>
</tr>
<tr>
<td>NEO FFI A</td>
</tr>
<tr>
<td>PCS Rumination</td>
</tr>
<tr>
<td>PCS Magnification</td>
</tr>
<tr>
<td>PCS Helplessness</td>
</tr>
<tr>
<td>PCS Total</td>
</tr>
<tr>
<td>BriefCOPE SD</td>
</tr>
<tr>
<td>BriefCOPE AC</td>
</tr>
<tr>
<td>BriefCOPE D</td>
</tr>
<tr>
<td>BriefCOPE SU</td>
</tr>
<tr>
<td>BriefCOPE ES</td>
</tr>
<tr>
<td>BriefCOPE IS</td>
</tr>
<tr>
<td>BriefCOPE BD</td>
</tr>
<tr>
<td>BriefCOPE V</td>
</tr>
<tr>
<td>BriefCOPE PR</td>
</tr>
<tr>
<td>BriefCOPE P</td>
</tr>
<tr>
<td>BriefCOPE H</td>
</tr>
<tr>
<td>BriefCOPE A</td>
</tr>
<tr>
<td>BriefCOPE R</td>
</tr>
<tr>
<td>BriefCOPE SB</td>
</tr>
</tbody>
</table>

*Note. NEO-FFI = NEO-Five Factor Inventory; N = neuroticism; E = extraversion; O = openness to experience; C = conscientiousness; A = agreeableness; PCS = Pain Catastrophizing Scale; SD = self-distraction; AC= active coping; D = denial; SU = substance use; ES = use of emotional support; IS = use of instrumental support; BD = behavioral disengagement; V = venting; PR = positive reframing; H = humor; A = acceptance; R = religion; SB = self-blame. *Significance of the comparison between follow-up sample and drop-outs as indicated by t-tests.
3.4 Statistical Analyses

The following sections outline the statistical strategy applied to test the hypotheses in section 2.6. To start with, section 3.4.1 details the operationalization of the theoretical constructs investigated in this study. The following data analysis was conducted in three steps. In the preliminary data screening (cf. section 3.4.2) the general assumptions of multiple and logistic regression analyses were tested to decide on the appropriate statistic approach for this thesis. The main data analysis was separated into a baseline analysis using the complete sample of N=112 (cf. section 3.4.3) and a follow-up analysis with the reduced sample size of N=68 (cf. section 3.4.4). Section 3.4.5 provides some methodological background knowledge on logistic regressions to facilitate the understanding of the reported results. All analyses were carried out using IBM SPSS Statistics 21.0.0.0.

3.4.1 Operationalization

Table 5 explains, how the theoretical constructs referred to in the hypotheses in section 2.6 were operationalized in this study. It contains a list of all variables measuring the earlier introduced constructs. Variable definitions, information on the questionnaire used for measurement and the scale of measurement are provided. The exact use of the variables in the statistical procedures is detailed in the sections 3.4.3 and 3.4.4.

<table>
<thead>
<tr>
<th>Construct</th>
<th>Variable Name</th>
<th>Definition</th>
<th>Questionnaire</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occurrence of Headache</strong></td>
<td>MIDAS Headache t1</td>
<td>Presence of headache within the last 3 months before surgery</td>
<td>MIDAS t1</td>
<td>Dichotomous (Yes, No)</td>
</tr>
<tr>
<td></td>
<td>MIDAS Headache t2</td>
<td>Presence of headache within the last 3 months before follow-up investigation</td>
<td>MIDAS t2</td>
<td>Dichotomous (Yes, No)</td>
</tr>
<tr>
<td></td>
<td>EHI Headache t1</td>
<td>Presence of headache at the time of the baseline investigation</td>
<td>EHI t1</td>
<td>Dichotomous (Yes, No)</td>
</tr>
<tr>
<td></td>
<td>EHI Headache t2</td>
<td>Presence of headache at the time of the follow-up investigation</td>
<td>EHI t2</td>
<td>Dichotomous (Yes, No)</td>
</tr>
<tr>
<td>Construct</td>
<td>Variable Name</td>
<td>Definition</td>
<td>Questionnaire</td>
<td>Scale</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Disability due to Headache</td>
<td>MIDAS Score t1</td>
<td>Impairment of daily activities within the last 3 months before surgery</td>
<td>MIDAS t1 (Total Score)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>MIDAS Score t2</td>
<td>Impairment of daily activities within the last 3 months before follow-up</td>
<td>MIDAS t2 (Total Score)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>MIDAS Grade t1</td>
<td>Grade of impairment of daily activities within the last 3 months before surgery</td>
<td>MIDAS t1 (Grade)</td>
<td>Ordinal</td>
</tr>
<tr>
<td></td>
<td>MIDAS Grade t2</td>
<td>Grade of impairment of daily activities within the last 3 months before follow-up</td>
<td>MIDAS t2 (Grade)</td>
<td>Ordinal</td>
</tr>
<tr>
<td></td>
<td>MIDAS Disability t1</td>
<td>Category of impairment of daily activities within the last 3 months before surgery</td>
<td>MIDAS t1 (Category)</td>
<td>Dichotomous</td>
</tr>
<tr>
<td></td>
<td>MIDAS Disability t2</td>
<td>Category of impairment of daily activities within the last 3 months before follow-up</td>
<td>MIDAS t2 (Category)</td>
<td>Dichotomous</td>
</tr>
<tr>
<td></td>
<td>ΔMIDAS</td>
<td>Difference between impairment of daily activities before surgery and after surgery</td>
<td>MIDAS Score t1 - MIDAS Score t2</td>
<td>Interval</td>
</tr>
<tr>
<td>Personality</td>
<td>NEO-FFI N</td>
<td>Neuroticism</td>
<td>NEO-FFI (Neuroticism Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI E</td>
<td>Extraversion</td>
<td>NEO-FFI (Extraversion Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI O</td>
<td>Openness to Experience</td>
<td>NEO-FFI (Openness to Experience Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI C</td>
<td>Conscientiousness</td>
<td>NEO-FFI (Conscientiousness Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI A</td>
<td>Agreeableness</td>
<td>NEO-FFI (Agreeableness Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td>Pain Catastrophizing</td>
<td>PCS Total</td>
<td>Pain Catastrophizing</td>
<td>PCS (Total Score)</td>
<td>Interval</td>
</tr>
<tr>
<td>Stress Coping</td>
<td>BriefCOPE D</td>
<td>Denial</td>
<td>BriefCOPE (Denial Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>BriefCOPE BD</td>
<td>Behavioral Disengagement</td>
<td>BriefCOPE (Behavioral Disengagement Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>BriefCOPE SB</td>
<td>Self-Blame</td>
<td>BriefCOPE (Self-Blame Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>BriefCOPE PR</td>
<td>Positive Reframing</td>
<td>BriefCOPE (Positive Reframing Scale)</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td>BriefCOPE H</td>
<td>Humor</td>
<td>BriefCOPE (Humor Scale)</td>
<td>Interval</td>
</tr>
</tbody>
</table>

*Note. NEO-FFI = NEO-Five Factor Inventory; MIDAS = Migraine Disability Assessment; EHI = Essen Headache Inventory; PCS = Pain Catastrophizing Scale.*
3.4.2 Preliminary Data Screening

To test for violations of the general assumptions of multiple and logistic regression analyses several preliminary analyses were calculated.

**Multiple Regression.** In order to conduct multiple regressions, linearity, normality and homoscedasticity of the included variables are required. Also, absence of extreme outliers, absence of multicollinearity and independence of errors are assumed.

Visual screening of the residual scatterplots of the planned regression models indicated severe violations of the assumption of normality and homoscedasticity. Inspection of the histograms of all included variables revealed skewness and kurtosis in the distributions of BriefCOPE D, BriefCOPE BD, BriefCOPE SB, BriefCOPE H and MIDAS Score. SPSS skewness and kurtosis statistics confirmed the visual impression. An attempted logarithmic transformation of the variables did not improve the distributions.

Boxplots were screened for univariate outliers. Extreme outliers were prominent in the variables BriefCOPE D, BriefCOPE BD and MIDAS Score. Mahalanobi’s Distance was calculated for each regression model to detect multivariate outliers. With a criterion of $\chi^2(5)=.001$ and $\chi^2(6)=.001$, respectively, no multivariate outliers were detected.

Multicollinearity was judged by evaluation of condition indices and variance proportions for the regression models. A condition index > 30 and a variance proportion > 0.50 was considered to be an indication of multicollinearity. Multicollinearity was not confirmed.

Independence of errors was evaluated by Durbin-Watson statistics for each regression model. All Durbin-Watson coefficients were close to 2 and gave no indication of autocorrelation of errors.

**Logistic Regression.** Logistic regression has no assumptions about the distribution of the predictor variables. It assumes, however, the absence of multicollinearity, in addition to the linearity of the logit.

Since multicollinearity concerns only predictor variables and is independent of the criterion variable, the results from the multicollinearity analysis in the multiple regression models can be transferred onto the logistic regression. Absence of multicollinearity can thus be assumed.
Linearity of the logit, i.e. the assumption of a linear relationship between the predictors and the logit transform of the criterion variable, was tested using the Box-Tidwell approach. Therefore, the natural logarithm of each predictor variable was calculated and interactions between the predictor variables and their natural logarithm were entered into the logistic regression model. None of the interactions was significant and, thus, linearity of the logit can be assumed.

In summary, the data screening revealed severe violations of the assumptions for multiple regression analyses, while all requirements for logistic regressions were met. Also, the somewhat reduced sample sizes in the analyses with the amended questionnaire set from Phase B suggested logistic regression to be the more appropriate approach. It was, therefore, decided to follow a logistic regression approach.

3.4.3 Baseline Analyses

To start with, headache characteristics before surgery (t1) are presented descriptively. For all interval scaled data means (M) and standard deviations (SD) are given. For categorical data absolute and relative frequencies, minima (MIN) and maxima (MAX) are reported.

Preceding the logistic regression, all potential influencing factors were correlated to the outcome variables by means of the point-biserial correlation coefficient $r_{pb}$. Predictors were only entered into the subsequent regression model, if they were either necessary to test the theoretically derived hypotheses or they were significantly correlated to the outcome variable. Additionally, the intercorrelations between the predictor variables were analyzed using Pearson’s correlation coefficient $r$ (cf. Table B1 in the appendix).

In order to test the influence of psychosocial factors on headache occurrence, stepwise logistic regression was then conducted, using the chosen psychosocial questionnaire scores from NEO-FFI, PCS and BriefCOPE as predictor variables and the occurrence of headache in the last 3 months as stated by the patients in the MIDAS questionnaire (MIDAS Headache t1) as the outcome variable. The criterion for the inclusion of predictors was set by default at $p<0.05$ for the $X^2$-statistic. The criterion was lowered to $p<0.10$, if the first model run did not yield significant results.

Thereafter, the influence of psychosocial factors on headache severity was investigated. Therefore, the MIDAS Score was transferred into a categorical outcome variable (MIDAS Disability t1) with two categories (0=no/mild disability, 1=moderate/severe disability). Again, questionnaire scores from NEO-FFI, PCS and BriefCope were used as predictor variables. To minimize the loss of data, the
logistic regression analyses of Phase A and Phase B of the study were carried out independent of each other in separate regression models.

### 3.4.4 Follow-up Analyses

In accordance with the baseline analyses, the follow-up analysis first provides a descriptive characterization of changes in headache after surgery (t2). Again, for interval scaled data M and SD and for categorical data absolute and relative frequencies, MIN and MAX are reported.

To evaluate whether headache frequency was reduced after surgery, a McNemar’s test was conducted on headache occurrence as stated in the MIDAS-questionnaire before (MIDAS Headache t1) and after treatment (MIDAS Headache t2). McNemar’s test is an adaption of a $\chi^2$-statistic to detect differences in a dichotomous outcome variable in a paired sample and, therefore, appropriate for a within-subject design. A cross table with absolute and relative frequencies, McNemar’s $\chi^2$-value, degrees of freedom (df) and the significance coefficient $p$ is given in the results section.

Changes in disability due to headache after surgery were assessed by a t-test for paired samples with the MIDAS Score as the dependent variable. M, SD and t-values and the significance coefficient $p$ are reported. For small sample sizes an additional non-parametric test, the Wilcoxon signed-rank test, was calculated to check the robustness of the t-test results.

Taking into account the modest sample size of the follow-up sample, no further regression models were contrived to find out whether the individual change in headache severity could be predicted by psychosocial factors (Hypothesis 5). Data analysis was limited to Pearson’s correlation in this section. To that end, $\Delta$MIDAS was calculated from the difference between the MIDAS Score t2 and MIDAS Score t1 and then correlated to the psychosocial factors. The correlation coefficient $r$ and the significance coefficient $p$ are reported.

### 3.4.5 Methodological Background: Logistic Regression

The following section explains the fundamental terms of logistic regression in order to facilitate the understanding of this study’s results. For a more comprehensive explanation of logistic regression refer to (Tabachnick, 2007).

Logistic regression is a regression analysis adapted for dichotomous outcome. It is based on a modification of the regular multiple regression equation [1]
\[ y' = a + bx_1 + bx_2 + \cdots + b_kx_k \]

where \( y' \) is the predicted value for the outcome variable \( y \), \( a \) is a constant, \( x_1 \ldots k \) are the predictor variables and \( b_1 \ldots k \) are the regression coefficients.

In contrast to multiple regression, logistic regression does not predict the value of the outcome variable \( y \), but the probability of being in one of the two groups of the outcome variable (in this study \emph{Headache} vs. \emph{No Headache}). For this calculation, odds are used. Odds are the probability of one case being in the response group of the outcome variable (\( y = 1 \), i.e. \emph{Headache}) divided by the probability of being in the reference group (\( y = 0 \), i.e. \emph{No Headache}).

The logistic regression equation [2]

\[ \ln \left( \frac{\hat{y}}{1-\hat{y}} \right) = a + b_1x_1 + b_2x_2 + \cdots + b_kx_k \]

predicts the logarithm of the odds of \( y = 1 \), when \( \hat{y} \) denotes the predicted probability of \( y = 1 \), \( a \) is a constant, \( x_1 \ldots k \) are the predictor variables and \( b_1 \ldots k \) are the regression coefficients. By solving this equation for \( \hat{y} \) the probability for \( y = 1 \) (i.e. to have headache) can be predicted for each case:

\[ \hat{y}_i = \frac{e^{a + b_1x_{i1} + b_2x_{i2} + \cdots + b_kx_{ik}}}{1 + e^{a + b_1x_{i1} + b_2x_{i2} + \cdots + b_kx_{ik}}} \]

Parameter estimations for the constant \( a \) and the regression coefficients \( b_1 \ldots k \) are obtained by a maximum likelihood procedure.

The resulting regression model is evaluated by its goodness-of-fit, i.e. the strength of the relationship between the predictors and the outcome. Therefore, the full model with all predictors \( x_1 \ldots k \) is tested against a reduced model with only the constant \( a \) by means of the comparison of log-likelihoods. Log-likelihoods for both models are calculated by adding up the predicted probabilities \( \hat{y}_i \) for the actual outcomes \( y_i \) of all cases. If the log-likelihood for the full model is significantly higher than that of the reduced model, this implies a significant improvement of the prediction by adding the predictors from the full model. Significance of the difference between log-likelihoods is indicated by a \( \chi^2 \)-test.

Additionally, Cox & Snell \( R_{CS}^2 \) is reported to evaluate the amount of variance explained by the model. Unlike \( R^2 \) in multiple regression, Cox & Snell \( R_{CS}^2 \) tends to be much lower and cannot achieve the maximum value of 1. For easier interpretation, also Nagelkerke’s \( R_{MAX}^2 \) is provided.
$R^2_{MAX}$ adjusts $R^2_{CS}$ such that its values range from 0 to 1 with a value of 1 denoting a perfect variance explanation. It is interpreted similarly to $R^2$ in linear regressions, but does not exactly equal the percentage of explained variance.

If a well-fitting model is found, the single predictors $x_{1-k}$ are tested for their individual contribution to the model by a Wald-test. This is a $\chi^2$-statistic, which compares the squared regression coefficient $b_j^2$ with its squared standard error $SE_{b_j}^2$. If the test is significant for one of the regression coefficients, this indicates a significant contribution of the predictor to the model.

Odds ratios are given for significant regression coefficients. The odds ratio is the change in the odds to be in the response group, when the value of the predictor $x_j$ increases by one unit. It can be interpreted as the factor by which the odds are multiplied when $x_j$ increases. It can also be understood as an effect size: the closer the odds ratio is to 1, the smaller is the effect of the predictor $x_j$.

Finally, the ability of the model to correctly predict the outcome group for individual cases is assessed. According to the estimation of the probability to belong to the response group $\hat{y}_i$, all cases are classified as belonging to the response or reference group using a cut-off criterion of $\hat{y}_i = 0.5$. Thus, the percentage of correctly classified patients, and of those falsely assigned to the response group (type I error) and those, falsely assigned to the reference group (type II error) can be calculated. The cutoff criterion of $\hat{y}_i = 0.5$ is a standard value and can be adjusted, if considered appropriate, to correctly identify more cases.
4 Results Part I – Headache before Surgery

4.1 Description of Headache Characteristics

**Occurrence.** Of the 112 patients questioned prior to surgery, 59 (52.7%) stated to have had headache within the last 3 months (*MIDAS Headache t1*). Headache occurred on average on 24.7 days (SD 24.6, *MIDAS Item #2*) and had an average severity of 52.12 (SD 23.7, *MIDAS Item #3*) on a scale from 0 to 100. Figure 5 shows the distribution of Items #2 and #3. 49 patients (43.8%) reported to have had headache at the time of filling in the questionnaire (*EHI Headache t1*).

**Disability due to Headache.** Those patients who had headache within the last three months reached an average *MIDAS Score t1* of 34.41 (SD 54.4). Minimal disability and severe disability were reported more frequently than mild and moderate disability. For logistic regression, patients were grouped with regard to their *MIDAS Grade t1*. Patients with *MIDAS Grade t1* I and II were grouped to *MIDAS Disability t1* none/mild and patients with *MIDAS Grade t1* III and IV to *MIDAS Disability t1* moderate/severe (cf. Table 6).

---

8 The study sample is the same as in the recent publication by Siegel et al., 2017 and in the unpublished thesis of R. Carneiro Scholl on biological predictors of headache in TSR. Parts of the sample description are, therefore, identical in all three publications in order to provide a comprehensive overview of the characteristics of the investigated study group. The reported results in the sample description are considered to be part of both dissertations.
Table 6

<table>
<thead>
<tr>
<th>MIDAS Grade</th>
<th>n (%)</th>
<th>MIDAS Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>minimal/infrequent (0-5)</td>
<td>29 (25.9%)</td>
<td>None/mild</td>
</tr>
<tr>
<td>Grade II:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (6-10)</td>
<td>1 (0.9%)</td>
<td>30 (26.8%)</td>
</tr>
<tr>
<td>Grade III:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate (11-20)</td>
<td>5 (4.5%)</td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Grade IV:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe (&gt;21)</td>
<td>24 (21.4%)</td>
<td>29 (25.9%)</td>
</tr>
</tbody>
</table>

Onset of Headache. 39 patients gave information about the time of first onset of headache. Of these, 18 had experienced onset of headache within the last year, 6 within the last 2 years, 6 within the last 5 years, 5 within the last 10 years and 4 more than 10 years ago. The maximum duration since headache onset and time of the study was 58.3 years⁹. On average, onset of headache occurred 6.02 (SD 13.26) years before filling in the questionnaires.

Figure 6

Absolute Frequencies of Headache Types according to the Essen Headache Inventory (EHI; n=45)

Note. Mixed headache types contains different combinations of the other categories.

⁹ The patient reported chronic migraine since childhood.
Headache Type. The most common headache type reported in the EHI was migraine without aura (n=21, 18.8%) followed by chronic daily headache (n=13, 11.6%), migraine with aura (n=12, 10.7%) and TTH (n=12, 10.7%; cf. Figure 6). 16 patients (14.3%) reported mixed headache types. Of these 8 exhibited a combination of 2 and 8 exhibited a combination of 3 or more different headache types. No specific combination was predominant in the sample (cf. Figure 6).

Location of Headache. Figure 7 depicts the frequency of headache locations in the MIDAS headzones module. Headache that was exclusively located frontally was most common. Of the 26 patients reporting frontal headache, 3 reported headache on their left frontal side only, 5 reported headache on their right frontal side only, and 18 reported headache on both sides.

4.2 Prediction of Headache by Personality

4.2.1 Prediction of Headache Occurrence

In the preliminary correlation analyses, there were no significant correlations between NEO-FFI personality scales and MIDAS Headache t1 (cf. Table 7). Nevertheless, to test the theoretically deduced hypotheses, all 5 variables were entered into the stepwise regression model with MIDAS Headache t1 as the criterion variable.
Table 7

Point-biserial Correlations between the Results of the NEO-FFI Questionnaire and the Occurrence of Headache (MIDAS Headache t1)

<table>
<thead>
<tr>
<th>NEO-FFI</th>
<th>n</th>
<th>rpb</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>110</td>
<td>0.138</td>
<td>0.150</td>
</tr>
<tr>
<td>E</td>
<td>110</td>
<td>-0.020</td>
<td>0.839</td>
</tr>
<tr>
<td>O</td>
<td>110</td>
<td>-0.033</td>
<td>0.731</td>
</tr>
<tr>
<td>C</td>
<td>110</td>
<td>0.164</td>
<td>0.086</td>
</tr>
<tr>
<td>A</td>
<td>110</td>
<td>-0.016</td>
<td>0.870</td>
</tr>
</tbody>
</table>

Note. NEO-FFI = Neo-Five Factor Inventory; N = neuroticism; E = extraversion; O = openness to experience; C = conscientiousness; A = agreeableness.

In the first model run with the standard statistical inclusion criterion of p≤0.05 in the $\chi^2$-statistic, none of the 5 factors was retained for the regression model (data not shown). Since p for NEO-FFI C was close to 0.05 ($\chi^2=2.976$, p=0.085), it was decided to run a second logistic regression analysis with a less conservative inclusion criterion of p ≤0.10 (cf. Table 8). Step I of the stepwise logistic regression then included NEO-FFI C as the only predictor variable. The test of the model against the constant-only model, however, revealed no significant improvement of the prediction through the addition of the predictor ($\chi^2=3.013$, p=0.083). In the second step NEO-FFI N was added as a predictor variable. Although the change in $\chi^2$ of 3.344 between Step I and Step II was not significant (p=0.067), the test of the full model against the constant-only model was statistically significant ($\chi^2=6.356$, p=0.042). This indicates, that conscientiousness and neuroticism together are able to predict the occurrence of headache. However, the amount of variance accounted for was extremely small with Cox & Snell $R^2$ of 0.056 and Nagelkerke $R^2_{MAX}$ of 0.075. With 53.6% of the cases predicted correctly, classification was equally unimpressive. It can be concluded, that the contribution of this regression model to the explanation of headache in patients with TSR is minimal.

Table 8

Logistic Regression Model of Headache Occurrence as a Function of Personality Variables: MIDAS Headache t1 yes vs. MIDAS Headache t1 no (n=110)

<table>
<thead>
<tr>
<th>Step</th>
<th>Retained factors</th>
<th>Change in $\chi^2$</th>
<th>p</th>
<th>$\chi^2$</th>
<th>p</th>
<th>Cox &amp; Snell $R^2$</th>
<th>Nagelkerke $R^2_{MAX}$</th>
<th>% right</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Constant + NEO-FFI C</td>
<td>3.013</td>
<td>0.083</td>
<td>3.013</td>
<td>0.083</td>
<td>0.027</td>
<td>0.036</td>
<td>53.6</td>
</tr>
<tr>
<td>2</td>
<td>Constant + NEO-FFI C + NEO-FFI N</td>
<td>3.344</td>
<td>0.067</td>
<td>6.356</td>
<td>0.042</td>
<td>0.056</td>
<td>0.075</td>
<td>53.6</td>
</tr>
</tbody>
</table>

Note. NEO-FFI = NEO-Five Factor Inventory; C = conscientiousness; N = neuroticism.
Parameter estimates from the second step (cf. Table 9) revealed that only NEO-FFI C contributed significantly to the prediction (Wald=3.958, p=0.047). This result indicates, that patients with higher values of conscientiousness in the NEO-FFI are more likely to develop headache prior to pituitary surgery. The odds ratio close to 1 implies a minimal effect size, though. The odds of headache occurrence for patients with 1 point more on NEO FFI C, multiply only by 1.067. In other words, the probability of having headache is only slightly elevated in highly conscientious patients compared to patients with low conscientiousness. Overall, the results confirm that personality variables predict the occurrence of headache in patients with TSR, but the relation is a small one.

Table 9
Parameter Estimates from the Logistic Regression Model of Headache Occurrence as a Function of Personality Variables:
MIDAS Headache t1 yes vs. MIDAS Headache t1 no (n=110)

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>p</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td>0.073</td>
<td>0.191</td>
<td>0.145</td>
<td>0.703</td>
<td>1.075</td>
</tr>
<tr>
<td>1</td>
<td>Constant</td>
<td>-1.490</td>
<td>0.942</td>
<td>2.516</td>
<td>0.113</td>
<td>0.224</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI C</td>
<td>0.052</td>
<td>0.031</td>
<td>2.893</td>
<td>0.089</td>
<td>1.053</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>-3.160</td>
<td>1.366</td>
<td>5.355</td>
<td>0.021</td>
<td>0.042</td>
</tr>
<tr>
<td>2</td>
<td>NEO-FFI C</td>
<td>0.064</td>
<td>0.032</td>
<td>3.958</td>
<td>0.047</td>
<td>1.067</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI N</td>
<td>0.062</td>
<td>0.035</td>
<td>3.160</td>
<td>0.075</td>
<td>1.064</td>
</tr>
</tbody>
</table>

Note. NEO-FFI = NEO-Five Factor Inventory; C = conscientiousness; N = neuroticism.

4.2.2 Prediction of Disability due to Headache

Correlation analyses between the scales from the NEO-FFI questionnaire and MIDAS Disability t1 revealed a strong relation between neuroticism and disability due to headache ($r_{pb}=0.368$, p=0.000; cf. Table 10). Accordingly, patients with moderate or severe headache exhibit higher levels of neuroticism than patients with none or mild headache. Again, for hypothesis testing, all 5 scales were entered as predictor variables into the regression model with MIDAS Disability t1 as the criterion variable.

Note that B for NEO-FFI C was slightly increased and reached significance in the second step. This is likely to be a sign of reciprocal suppression. Both NEO-FFI C and NEO-FFI N were positively correlated to the criterion and intercorrelated negatively (cf. Table B1 in the appendix). They thus enhance each other’s predictive ability by suppressing variance that is irrelevant to the prediction of the criterion.
Table 10

Point-biserial Correlations between the Results of the NEO-FFI Questionnaire and Disability due to Headache (MIDAS Disability t1)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>rpb</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEO-FFI N</td>
<td>110</td>
<td>0.368</td>
<td>0.000</td>
</tr>
<tr>
<td>NEO-FFI E</td>
<td>110</td>
<td>-0.052</td>
<td>0.591</td>
</tr>
<tr>
<td>NEO-FFI O</td>
<td>110</td>
<td>-0.089</td>
<td>0.353</td>
</tr>
<tr>
<td>NEO-FFI C</td>
<td>110</td>
<td>0.098</td>
<td>0.307</td>
</tr>
<tr>
<td>NEO-FFI A</td>
<td>110</td>
<td>-0.039</td>
<td>0.686</td>
</tr>
</tbody>
</table>

Note. NEO-FFI = Neo-Five Factor Inventory; N = neuroticism; E = extraversion; O = openness to experience; C = conscientiousness; A = agreeableness.

In the stepwise logistic regression model, NEO-FFI N was retained as the only relevant predictor variable (cf. Table 11). The \( \chi^2 \)-test of the full model against the constant-only model was highly significant, implying a clear improvement of the prediction of disability due to headache through the addition of neuroticism as a predictor. The full model explained a moderate amount of variance (Cox & Snell \( R^2 = 0.137 \), Nagelkerke \( R^2_{\text{MAX}} = 0.200 \)). With an overall percentage of correctly predicted cases of 75.5%, the classification was comparatively good. However, even the constant-only model successfully predicted 73.6% of the cases, and only an improvement of 1.9% was due to the inclusion of NEO-FFI N as a predictor. The regression model thus contributes moderately to the explanation of disability due to headache in patients with TSR.

Table 11

Logistic Regression Model of Disability due to Headache as a Function of Personality Variables: MIDAS Disability t1 no/little vs. moderate/severe (n=110)

<table>
<thead>
<tr>
<th>Step</th>
<th>Retained factors</th>
<th>Change in ( \chi^2 )</th>
<th>p</th>
<th>( \chi^2 )</th>
<th>p</th>
<th>Cox &amp; Snell ( R^2_{\text{CS}} )</th>
<th>Nagelkerke ( R^2_{\text{MAX}} )</th>
<th>% right</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73.6</td>
</tr>
<tr>
<td>1</td>
<td>Constant</td>
<td></td>
<td>+</td>
<td>16.226</td>
<td>0.000</td>
<td>16.226</td>
<td>0.000</td>
<td>0.137</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. NEO-FFI = Neo-Five Factor Inventory; N = neuroticism.
Table 12 shows the parameter estimates from the logistic regression for the prediction of disability due to headache. According to the highly significant Wald-test, NEO-FFI N reliably predicted disability due to headache ($\chi^2 = 12.626, p = 0.000$). A one-unit change on NEO-FFI N resulted in a multiplication of the odds of experiencing moderate or severe headache by 1.179. This implies that the probability of experiencing a disability due to headache is moderately elevated in patients with high neuroticism compared to patients with low neuroticism. In summary, the predictive value of personality variables with regard to disability due to headache in patients with TSR appears to be moderate.

### Table 12

**Parameter Estimates from the logistic Regression Model of Headache Disability as a Function of Personality Variables:**

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>p</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td>-1.027</td>
<td>0.216</td>
<td>22.530</td>
<td>0.000</td>
<td>0.358</td>
</tr>
<tr>
<td>1</td>
<td>Constant</td>
<td>-4.700</td>
<td>1.098</td>
<td>18.324</td>
<td>0.000</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>NEO-FFI N</td>
<td>0.165</td>
<td>0.046</td>
<td>12.626</td>
<td>0.000</td>
<td>1.179</td>
</tr>
</tbody>
</table>

*Note. NEO-FFI = Neo-Five Factor Inventory; N = neuroticism.*

### 4.3 Prediction of Headache by Stress Coping and Pain Catastrophizing

#### 4.3.1 Prediction of Headache Occurrence

Table 13 shows point-biserial correlations between questionnaire scales from the BriefCOPE and the PCS and MIDAS Headache t1. PCS Total ($r_{pb}=0.273$, p=0.032), BriefCOPE SU ($r_{pb}=-0.250$, p=0.037) and BriefCOPE PR ($r_{pb}=0.262$, p=0.028) were significantly related to MIDAS Headache t1. This indicates that headache in patients with TSR is associated with higher levels of pain catastrophizing and positive reframing but with less substance use. All three variables with significant correlation to the criterion variable MIDAS Headache t1 were entered into the logistic regression model for the prediction of headache occurrence. As planned, BriefCOPE D, BriefCOPE H, BriefCOPE BD and BriefCOPE SB were added as predictor variables to test the theoretically deduced hypotheses.
Table 13

Point-biserial Correlations between MIDAS Headache t1 and Results of the PCS and BriefCOPE Questionnaires

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>rpb</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS Total</td>
<td>62</td>
<td>0.273</td>
<td>0.032</td>
</tr>
<tr>
<td>BriefCOPE SD</td>
<td>70</td>
<td>0.176</td>
<td>0.146</td>
</tr>
<tr>
<td>BriefCOPE AC</td>
<td>69</td>
<td>0.201</td>
<td>0.097</td>
</tr>
<tr>
<td>BriefCOPE D</td>
<td>69</td>
<td>0.016</td>
<td>0.899</td>
</tr>
<tr>
<td>BriefCOPE SU</td>
<td>70</td>
<td>-0.250</td>
<td>0.037</td>
</tr>
<tr>
<td>BriefCOPE ES</td>
<td>70</td>
<td>0.050</td>
<td>0.684</td>
</tr>
<tr>
<td>BriefCOPE IS</td>
<td>69</td>
<td>0.113</td>
<td>0.357</td>
</tr>
<tr>
<td>BriefCOPE BD</td>
<td>68</td>
<td>-0.033</td>
<td>0.791</td>
</tr>
<tr>
<td>BriefCOPE V</td>
<td>69</td>
<td>-0.095</td>
<td>0.439</td>
</tr>
<tr>
<td>BriefCOPE PR</td>
<td>70</td>
<td>0.262</td>
<td>0.028</td>
</tr>
<tr>
<td>BriefCOPE P</td>
<td>70</td>
<td>0.068</td>
<td>0.574</td>
</tr>
<tr>
<td>BriefCOPE H</td>
<td>70</td>
<td>0.157</td>
<td>0.195</td>
</tr>
<tr>
<td>BriefCOPE A</td>
<td>68</td>
<td>-0.039</td>
<td>0.751</td>
</tr>
<tr>
<td>BriefCOPE R</td>
<td>69</td>
<td>0.067</td>
<td>0.586</td>
</tr>
<tr>
<td>BriefCOPE SB</td>
<td>70</td>
<td>0.074</td>
<td>0.544</td>
</tr>
</tbody>
</table>

Note. PCS = Pain Catastrophizing Scale; SD = self-distraction; AC = active coping; D = denial; SU = substance use; ES = use of emotional support; IS = use of instrumental support; BD = behavioral disengagement; V = venting; PR = positive reframing; P = planning; H = humor; A = acceptance; R = religion; SB = self-blame.

Of all entered predictor variables, only PCS Total was retained for the regression model (cf. Table 14). As indicated by the significant $\chi^2$-test of the full model against the constant-only model ($\chi^2$=4.083, p=0.043), the prediction of headache occurrence was significantly improved by the addition of pain catastrophizing as a predictor. The amount of variance accounted for was small (Cox & Snell $R^2$=0.067; Nagelkerke $R^2_{MAX}$=0.090), but the classification was improved by 9.5%, resulting in 64.4% of correctly predicted cases. The contribution of this regression model to the explanation of headache occurrence in patients with TSR is thus a small one.

Table 14

Logistic Regression Model of Headache Occurrence as a Function of Stress Coping and Pain Catastrophizing: MIDAS Headache t1 yes vs. MIDAS Headache t1 no (n=59)

<table>
<thead>
<tr>
<th>Step</th>
<th>Retained factors</th>
<th>Change in $\chi^2$</th>
<th>$p$</th>
<th>$\chi^2$</th>
<th>$p$</th>
<th>Cox &amp; Snell $R^2$</th>
<th>Nagelkerke $R^2_{MAX}$</th>
<th>% right</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55.9</td>
</tr>
<tr>
<td>1</td>
<td>Constant + PCS Total</td>
<td>4.083</td>
<td>0.043</td>
<td>1.083</td>
<td>0.043</td>
<td>0.067</td>
<td>0.090</td>
<td>64.4</td>
</tr>
</tbody>
</table>

Note. PCS = Pain Catastrophizing Scale.
The parameter estimates from the regression model argue for a small predictive value of pain catastrophizing (cf. Table 15) for the prediction of headache occurrence. The Wald test for the individual contribution of PCS Total just failed to reach significance ($\chi^2=3.727$, $p=0.054$) and the odds ratio of 1.051 showed little change in the likelihood of headache occurrence through a one-unit change in the PCS. This indicates, that the probability of having headache is not noticeably increased by higher pain catastrophizing. The association between pain catastrophizing and headache occurrence in patients with TSR is, in summary, not very strong.

Table 15
Parameter Estimates from the logistic Regression Model of Headache Occurrence as a Function of Stress Coping and Pain Catastrophizing: MIDAS Headache t1 yes vs. MIDAS Headache t1 no (n=59)

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>p</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td>-0.238</td>
<td>0.262</td>
<td>0.827</td>
<td>0.363</td>
<td>0.788</td>
</tr>
<tr>
<td>1</td>
<td>Constant</td>
<td>1.067</td>
<td>0.513</td>
<td>4.408</td>
<td>0.036</td>
<td>0.341</td>
</tr>
<tr>
<td></td>
<td>PCS Total</td>
<td>0.050</td>
<td>0.026</td>
<td>3.727</td>
<td>0.054</td>
<td>1.051</td>
</tr>
</tbody>
</table>

Note. PCS = Pain Catastrophizing Scale.

4.3.2 Prediction of Disability due to Headache

The preliminary correlation analyses for the coping model showed that PCS Total ($r_{pb}=0.433$, $p=0.000$), BriefCOPE SU ($r_{pb}=-0.242$, $p=0.044$), BriefCOPE PR ($r_{pb}=0.296$, $p=0.013$) and BriefCOPE H ($r_{pb}=0.390$, $p=0.001$) were significantly related to MIDAS Disability t1 (cf. Table 16). These results indicate that moderate or severe disability due to headache is accompanied by higher levels of pain catastrophizing, positive reframing and humor, but by a lesser extent of substance use. The four variables with a significant correlation to the criterion variable MIDAS Disability t1 were entered as predictor variables into the logistic regression model. Additionally, BriefCOPE D, BriefCOPE BD and BriefCOPE SB were included as predictors to test the theoretically deduced hypotheses.
Table 16

Point-biserial Correlations between MIDAS Disability t1 and Results of the PCS and BriefCOPE Questionnaires

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>r_{pb}</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS Total</td>
<td>62</td>
<td>0.433</td>
<td>0.000</td>
</tr>
<tr>
<td>BriefCOPE SD</td>
<td>70</td>
<td>0.157</td>
<td>0.193</td>
</tr>
<tr>
<td>BriefCOPE AC</td>
<td>69</td>
<td>0.085</td>
<td>0.487</td>
</tr>
<tr>
<td>BriefCOPE D</td>
<td>69</td>
<td>0.112</td>
<td>0.358</td>
</tr>
<tr>
<td>BriefCOPE SU</td>
<td>70</td>
<td>-0.242</td>
<td>0.044</td>
</tr>
<tr>
<td>BriefCOPE ES</td>
<td>70</td>
<td>0.078</td>
<td>0.521</td>
</tr>
<tr>
<td>BriefCOPE IS</td>
<td>69</td>
<td>-0.170</td>
<td>0.162</td>
</tr>
<tr>
<td>BriefCOPE BD</td>
<td>68</td>
<td>0.223</td>
<td>0.068</td>
</tr>
<tr>
<td>BriefCOPE V</td>
<td>69</td>
<td>-0.040</td>
<td>0.743</td>
</tr>
<tr>
<td>BriefCOPE PR</td>
<td>70</td>
<td>0.296</td>
<td>0.013</td>
</tr>
<tr>
<td>BriefCOPE P</td>
<td>70</td>
<td>0.016</td>
<td>0.897</td>
</tr>
<tr>
<td>BriefCOPE H</td>
<td>70</td>
<td>0.390</td>
<td>0.001</td>
</tr>
<tr>
<td>BriefCOPE A</td>
<td>68</td>
<td>-0.087</td>
<td>0.481</td>
</tr>
<tr>
<td>BriefCOPE R</td>
<td>69</td>
<td>0.088</td>
<td>0.472</td>
</tr>
<tr>
<td>BriefCOPE SB</td>
<td>70</td>
<td>0.231</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Note. PCS = Pain Catastrophizing Scale; SD = self-distraction; AC = active coping; D = denial; SU = substance use; ES = use of emotional support; IS = use of instrumental support; BD = behavioral disengagement; V = venting; PR = positive reframing; P = planning, H = humor; A = acceptance; R = religion; SB = self-blame.

Table 17 summarizes the steps from the logistic regression model for the prediction of MIDAS Disability t1. In the first step PCS Total was retained as the only predictor. The highly significant \(\chi^2\)-test of the step I model against the constant-only model (\(\chi^2=10.786, p=0.001\)) indicated a clear improvement of the prediction through the inclusion of PCS Total alone. With Cox & Snell \(R_{CS}^2\) of 0.167 and Nagelkerke \(R_{MAX}^2\) of 0.246, the amount of explained variance was already relatively high. Classification improved from 74.6% correctly predicted cases in the constant-only model to 81.4% in the step I model. In the second step, BriefCOPE H was added as a second predictor, resulting in a further improvement of the prediction as indicated by the significant change of \(\chi^2\) by 8.266 (\(p=0.004\)). The overall model explained a satisfactory amount of variance (Cox & Snell \(R_{CS}^2 = 0.276\), Nagelkerke \(R_{MAX}^2 = 0.407\)) and classified 86.4% of all cases correctly. These results give evidence of a substantial contribution of this regression model to the explanation of disability due to headache in patients with TSR.
Table 17
Logistic Regression Model of Disability due to Headache as a Function of Stress Coping and Pain Catastrophizing: MIDAS Disability t1 no/little vs moderate/severe (n=59)

<table>
<thead>
<tr>
<th>Step</th>
<th>Retained factors</th>
<th>Change in $\chi^2$</th>
<th>$\chi^2$</th>
<th>p</th>
<th>Cox &amp; Snell $R^2$</th>
<th>Nagelkerke $R_{MAX}^2$</th>
<th>% right</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74.6</td>
</tr>
<tr>
<td>1</td>
<td>Constant + PCS Total</td>
<td>10.786</td>
<td>10.786</td>
<td>0.001</td>
<td>0.167</td>
<td>0.246</td>
<td>81.4</td>
</tr>
<tr>
<td>2</td>
<td>Constant + PCS Total + BriefCOPE H</td>
<td>8.266</td>
<td>19.052</td>
<td>0.004</td>
<td>0.276</td>
<td>0.407</td>
<td>86.4</td>
</tr>
</tbody>
</table>

Note. PCS = Pain Catastrophizing Scale; H = humor.

The parameter estimates from the second step of the model determined that both PCS Total (Wald=7.608, p=0.006) and BriefCOPE H (Wald=6.637, p=0.010) contributed significantly to the prediction of MIDAS Disability t1 (cf. Table 18). While a one-unit change in PCS Total multiplied the odds of experiencing moderate or severe headache by 1.106, a one-unit change in BriefCOPE H even doubled the odds. In other words, pain catastrophizing and humor as a coping strategy both increase the probability to experience disability due to headache considerably. Thus, pain catastrophizing and humor are both highly relevant predictors for disability due to headache in patients with TSR.

Table 18
Parameter Estimates from the logistic Regression Model of Headache Disability as a Function of Stress Coping and Pain Catastrophizing: MIDAS Disability t1 no/little vs. moderate/severe (n=59)

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>p</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Constant</td>
<td>-1.076</td>
<td>0.299</td>
<td>12.955</td>
<td>0.000</td>
<td>0.341</td>
</tr>
<tr>
<td>1</td>
<td>Constant</td>
<td>-2.868</td>
<td>0.741</td>
<td>14.963</td>
<td>0.000</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>PCS Total</td>
<td>0.096</td>
<td>0.033</td>
<td>8.533</td>
<td>0.003</td>
<td>1.100</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td>-5.384</td>
<td>1.396</td>
<td>14.875</td>
<td>0.000</td>
<td>0.005</td>
</tr>
<tr>
<td>2</td>
<td>PCS Total</td>
<td>0.101</td>
<td>0.037</td>
<td>7.608</td>
<td>0.006</td>
<td>1.106</td>
</tr>
<tr>
<td></td>
<td>BriefCOPE H</td>
<td>0.672</td>
<td>0.261</td>
<td>6.637</td>
<td>0.010</td>
<td>1.958</td>
</tr>
</tbody>
</table>

Note. PCS = Pain Catastrophizing Scale; H = humor.
5 Results Part II – Headache after Surgery

5.1 Description of Headache Characteristics

Headache Occurrence. Of the 68 patients who answered the follow-up questionnaires, 27 (39.7%) reported to have had headache within the last 3 months (MIDAS Headache t2). On average headache occurred on 18.4 days (SD 23.9, MIDAS t2 Item #2) and had an average severity of 41.4 (SD 18.1, MIDAS t2 Item #3) on a scale from 0 to 100. 23 patients (33.8%) reported to have headache at the time of the follow-up investigation (EHI Item #1).

Disability due to Headache. In those patients who reported to have experienced headache within the last three months in the follow-up questionnaires, the mean MIDAS Score t2 was 23.2 (SD 52.1). Minimal or infrequent disability was most prevalent after surgery (cf. Table 19). Only 3 patients stated to have missed worktime due to headache within the last three months.

Table 19

<table>
<thead>
<tr>
<th>MIDAS Grade t2</th>
<th>n (%)</th>
<th>MIDAS Disability t2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I: minimal/infrequent (0-5)</td>
<td>18 (66.7%)</td>
<td>none/mild 19 (70.4%)</td>
</tr>
<tr>
<td>Grade II: Mild (6-10)</td>
<td>1 (3.7%)</td>
<td>&gt;</td>
</tr>
<tr>
<td>Grade III: moderate (11-20)</td>
<td>2 (7.4%)</td>
<td>&gt;</td>
</tr>
<tr>
<td>Grade IV: severe (&gt;21)</td>
<td>6 (22.2%)</td>
<td>moderate/severe 8 (29.6%)</td>
</tr>
</tbody>
</table>

Headache Type. The most common headache type after surgery reported in the EHI was migraine without aura (n=8, 29.6%) followed by TTH (n=7, 25.9%), migraine with aura (n=5, 18.5%) and chronic daily headache (n=5, 18.5%; cf. Figure 8). In contrast to the baseline sample, there were no patients reporting chronic migraine or chronic TTH. 8 patients (29.6%) described mixed headache types, of these 4 had a combination of 2 and 4 of 3 or more different headache types. As in the baseline sample no specific combination of headache types was predominant.
Figure 8

Absolute Frequencies of Headache Types after Surgery according to the Essen Headache Inventory (EHI; n=23)

Note. Mixed headache types contains different combinations of the other categories.

Location of Headache. Most often, patients after surgery reported mixed headache locations with no clear pattern (n=10, 14.7%), followed by headache on the whole head (n=4, 5.9%) and left-sided headache (n=3, 4.4%). Only two patients reported frontal headache after surgery, both had headache on the left and on the right frontal side (cf. Figure 9).

Figure 9

Location of Headache as reported in the Migraine Disability Assessment (MIDAS) Headzones Module (n=21)
5.2 Changes in Headache Characteristics over Time

5.2.1 Changes in Headache Occurrence

Of those patients in the follow-up sample, who had had headache in the three months previous to surgery (n=34), 17 (50%) stated in the follow-up investigation that they had not had headache anymore within the last three months. On the other hand, 10 patients who did not have headache before, developed a new headache after surgery (29.7%). The McNemar’s test for the treatment effect was not significant (p=0.248; cf. Table 20). This result contradicts a reliable beneficial effect of neurosurgery on the occurrence of headache in patients with TSR.

Table 20
Comparison of Frequencies of Headache Occurrence in the Baseline and in the Follow-up Sample as indicated by McNemar’s test (n=68)

<table>
<thead>
<tr>
<th></th>
<th>MIDAS Headache t2</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>n</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>70.6%</td>
<td>29.4%</td>
</tr>
<tr>
<td>MIDAS Headache t1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>n</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>50.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Total</td>
<td>n</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>60.3%</td>
<td>39.7%</td>
</tr>
</tbody>
</table>

5.2.2 Changes in Disability due to Headache

Figure 10 shows the individual development of the patients’ disability due to headache from baseline to follow-up as indicated by the MIDAS Score t1 and the MIDAS Score t2. Cases are sorted by ∆MIDAS, so that patients whose headache worsened are shown on the left-hand side and patients with an improvement of headache can be seen on the right-hand side of the figure.

Of the 68 patients who answered the follow-up questionnaires, 8 (11.8%) reported that their disability due to headache had increased after surgery. Of these 5 (7.4%) had developed a new disability, while in 3 patients (n=4.4%) disability due to an already existent headache had worsened. Patients with a deterioration of headache had an average baseline MIDAS Score t1 of 25.2 (SD 42.8) and experienced a worsening by 45.1 points (SD 71.9).
Figure 10

*Individual Development of Disability due to Headache from Baseline to Follow-up as indicated by MIDAS Score t1 and MIDAS Score t2 (n=23)*

Note. Only patients that reported disability due to headache either at baseline or at follow-up are depicted.

All 45 patients (66.2%) who did not experience a change in disability in the course of the follow-up period stated that they neither suffered from disability due to headache before nor after surgery. Correspondingly, they had a mean MIDAS Score t1 and MIDAS Score t2 of 0.0 (SD 0.0).

The remaining 15 patients (22.1%) reported an improvement in disability due to headache after surgery. These patients had an average MIDAS Score t1 of 53.9 before surgery (SD 57.4) and a mean improvement by 49.7 points (SD 58.9). 13 patients (19.1%) experienced an improvement of at least 50%\textsuperscript{11}, 11 of them experienced a full decline of disability due to headache to a MIDAS Score t2 of 0.

The comparison of the mean MIDAS Scores before and after surgery did not reveal a significant improvement in the course of the follow-up period (p= 0.304; cf. Table 21). Also, a second paired

\textsuperscript{11} This result is of relevance for the estimation of prevalence of headache associated with TSR in the population. Cf. section 6.1.1 for a discussion.
t-test without those patients who did not report headache at all at t1 or t2 did not find a significant change (p=0.311). Since this subsample was too small to assume robust results in the t-test (n=23), an additional non-parametric test was calculated, which did not detect a significant effect either (Wilcoxon signed-rank test, p = 0.171). In summary, these results cannot confirm a beneficial effect of neurosurgery on disability due to headache in patients with TSR.

Table 21

*Paired t-tests for the Comparison of Disability due to Headache before and after Surgery as indicated by MIDAS Score t1 and MIDAS Score t2*

<table>
<thead>
<tr>
<th>Sample</th>
<th>n</th>
<th>M</th>
<th>SD</th>
<th>M</th>
<th>SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete follow-up sample</td>
<td>68</td>
<td>14.9</td>
<td>37.2</td>
<td>9.2</td>
<td>34.4</td>
<td>1.036</td>
<td>0.304</td>
</tr>
<tr>
<td>Patients with headache at t1 or t2</td>
<td>23</td>
<td>43.9</td>
<td>53.6</td>
<td>27.2</td>
<td>55.6</td>
<td>1.038</td>
<td>0.311</td>
</tr>
</tbody>
</table>

5.3 Relation between Personality and Changes in Disability due to Headache

Table 22 shows the results from the correlation analyses between ∆MIDAS and the NEO FFI personality scales. ∆MIDAS was significantly correlated to NEO-FFI E (r=0.398, p=0.001) and nearly significantly correlated to NEO FFI A (r=0.208, p=0.094). NEO-FFI N was correlated inversely to ∆MIDAS (r=-0.248, p=0.045). Thus, the more extraverted and agreeable and the less neurotic patients were at t1, the bigger was the extent of improvement of headache they experienced through surgery.

Table 22

*Pearson Correlations between ∆MIDAS and Results of the NEO FFI Questionnaire*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEO-FFI N</td>
<td>66</td>
<td>-0.248</td>
<td>0.045</td>
</tr>
<tr>
<td>NEO-FFI E</td>
<td>66</td>
<td>0.398</td>
<td>0.001</td>
</tr>
<tr>
<td>NEO-FFI O</td>
<td>66</td>
<td>0.133</td>
<td>0.285</td>
</tr>
<tr>
<td>NEO-FFI C</td>
<td>66</td>
<td>0.177</td>
<td>0.154</td>
</tr>
<tr>
<td>NEO-FFI A</td>
<td>66</td>
<td>0.208</td>
<td>0.094</td>
</tr>
</tbody>
</table>

*Note.* NEO-FFI = Neo-Five Factor Inventory; N = neuroticism; E = extraversion; O = openness to experience; C = conscientiousness; A = agreeableness.
5.4 Relation between Stress Coping, Pain Catastrophizing and Disability due to Headache

Of all the investigated coping strategies from the BriefCOPE questionnaire, only BriefCOPE BD ($p=-0.514$, $p=0.001$) and BriefCOPE H ($r=-0.441$, $p=0.005$) were correlated to $\Delta$MIDAS (cf. Table 23). Accordingly, higher levels of behavioral disengagement and humor at t1 are associated with little change or a worsening of disability due to headache.

Table 23

Pearson Correlations between $\Delta$MIDAS and results of the PCS and BriefCOPE Questionnaires

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS Total</td>
<td>35</td>
<td>-0.264</td>
<td>0.126</td>
</tr>
<tr>
<td>BriefCOPE SD</td>
<td>39</td>
<td>-0.082</td>
<td>0.620</td>
</tr>
<tr>
<td>BriefCOPE AC</td>
<td>39</td>
<td>-0.037</td>
<td>0.821</td>
</tr>
<tr>
<td>BriefCOPE D</td>
<td>39</td>
<td>-0.083</td>
<td>0.616</td>
</tr>
<tr>
<td>BriefCOPE SU</td>
<td>39</td>
<td>0.164</td>
<td>0.320</td>
</tr>
<tr>
<td>BriefCOPE ES</td>
<td>39</td>
<td>0.073</td>
<td>0.657</td>
</tr>
<tr>
<td>BriefCOPE IS</td>
<td>39</td>
<td>0.051</td>
<td>0.758</td>
</tr>
<tr>
<td>BriefCOPE BD</td>
<td>39</td>
<td>-0.514</td>
<td>0.001</td>
</tr>
<tr>
<td>BriefCOPE V</td>
<td>39</td>
<td>0.108</td>
<td>0.515</td>
</tr>
<tr>
<td>BriefCOPE PR</td>
<td>39</td>
<td>-0.112</td>
<td>0.499</td>
</tr>
<tr>
<td>BriefCOPE P</td>
<td>39</td>
<td>0.050</td>
<td>0.762</td>
</tr>
<tr>
<td>BriefCOPE H</td>
<td>39</td>
<td>-0.441</td>
<td>0.005</td>
</tr>
<tr>
<td>BriefCOPE A</td>
<td>38</td>
<td>0.165</td>
<td>0.322</td>
</tr>
<tr>
<td>BriefCOPE R</td>
<td>38</td>
<td>0.090</td>
<td>0.591</td>
</tr>
<tr>
<td>BriefCOPE SB</td>
<td>39</td>
<td>-0.256</td>
<td>0.116</td>
</tr>
</tbody>
</table>

Note. PCS = Pain Catastrophizing Scale; SD = self-distraction; AC= active coping; D = denial; SU = substance use; ES = use of emotional support; IS = use of instrumental support; BD = behavioral disengagement; V = venting; PR = positive reframing; P=planning; H = humor; A = acceptance; R = religion; SB = self-blame.
6 Discussion

This prospective study aimed at identifying the psychological factors that might influence the development of headache in patients with TSR. To that end, detailed headache characteristics before and after surgery, personality traits, coping strategies and pain catastrophizing were investigated in 112 patients with TSR. The influence of the three investigated psychological factors on headache occurrence and disability due to headache was analyzed in logistic regression models. Treatment response (i.e. change in disability due to headache after surgery) was correlated to the three psychological factors.

The following discussion starts with a description of headache before and after surgery, including an evaluation of treatment success with regard to headache (section 6.1). The main part of the discussion, section 6.2, reviews the investigated psychological factors and draws a conclusion towards the proposed biopsychosocial model. Thereafter, the implications of the present results for clinical practice (cf. section 6.3) and future research 6.4 (cf. section 7.4) are discussed. The discussion concludes with reflections on the limitations of the study (cf. section 6.5) and a brief summary of the main implications of this doctoral thesis (cf. section 6.6).

6.1 Development of Headache in Patients with TSR

6.1.1 Prevalence

In this study group, 52.7% of the patients with TSR reported headache within the last three months before pituitary surgery and 44% reported current headache at the time of the study. The prevalence of headache in patients with TSR varied considerably in previous studies (cf. section 2.4.1). The prevalence of 52.7% in the present study is a little lower than expected from the majority of the previous studies, which mostly found prevalences above 60% (e.g. Levy et al., 2004, Gondim et al., 2009, Dimopoulou et al., 2014). The even lower prevalence of 44% patients with headache at the time of the investigation may indicate a substantial natural fluctuation of headache in patients with TSR even over the course of weeks. This fluctuation could be accountable for some of the variance in the previously found prevalences. It should be considered in future estimations of the prevalence of headache in patients with TSR.

Prevalence estimations of headache in patients with TSR also suffer from uncertainties in the diagnosis of TSR-attributed headache. According to the ICHD-3 guideline (IHS, 2013), a causal link between neoplasm and headache can only be assumed if headache develops in temporal relation
to the neoplasm or worsens or improves in parallel to the neoplasm (cf. section 2.1.2.2). In the case of TSR, the temporal relation of headache development to the development of the tumor is difficult to prove. At the time of the diagnosis of TSR, it is unclear how long the undetected tumor had already been there. As a consequence, it is unclear at which point in time before the diagnosis of TSR headache should set in or worsen to be evidence of a causal link. Most previous prevalence studies thus either ignored the temporal relation completely (e.g. Gondim et al., 2009) or had to rely on an arbitrarily set time criterion. For example, Levy et al. defined, that headache had to be closely related to the MRI diagnosing TSR (Levy et al., 2004), whereas Arafah et al. defined that headache had to occur in the 5 years prior to the diagnosis of TSR (Arafah et al., 2000). As these criteria are insufficient to clearly demonstrate a causal link between headache and TSR, these studies will likely have included primary headache disorders falsely diagnosed as headache attributed to TSR. This could have led to an overestimation of the prevalence of headache in TSR.

Schankin et al. tried to reduce this inaccuracy by applying a much stricter criterion for headache to qualify as attributable to pituitary adenoma. They defined that a) headache had to be present in the three months prior to surgery, b) medication overuse had to be ruled out and c) post-operative amelioration had to be at least 50% with respect to frequency and severity. With these criteria they found a significantly lower prevalence of 39.3% (Schankin et al., 2012). The inclusion of the improvement of headache after surgery into the defining criteria of headache attributed to TSR, as suggested by Schankin, requires a prospective study design. As one of the few prospective studies in this research field, the present thesis was able to apply the same criteria as Schankin. According to this strict definition, this thesis finds a very low prevalence of 19% headache attributed to TSR in the investigated sample (cf. section 5.2.2).

6.1.2 Headache Characteristics before Surgery

Patients in this study group presented with all different headache types and combinations of headache types. Migraine without aura was the most common form of headache, occurring in 18% of the patients, followed by chronic daily headache, reported by 11% of the patients. Those patients, who had headache, reported an average MIDAS Score of 34. 50% of them had none or mild and 50% had moderate to severe disability due to headache. Onset of headache was on

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12 These sections contain only a short evaluation of the headache characteristics as far as they are of relevance to the objectives of this thesis. A more in depth discussion of these results is left to the dissertation of R. Carneiro Scholl.
average 6 years before the time of the study, but the standard deviation was large. Headache was located frontally in most patients, but occurred in any other locations of the head as well.

In summary, the described headache characteristics were strikingly heterogeneous. All investigated headache parameters varied considerably between patients, despite the fact, that the study sample had been restricted to patients directly prior to first time surgery only. This result implies that there seems to be no distinct and easily definable headache type commonly associated with TSR. In this respect, our findings are in line with several older studies, which were equally unable to define a predominant kind of headache in patients with pituitary adenomas and other TSR (Abe et al., 1998, Levy et al., 2005, Gondim et al., 2009, Schankin et al., 2012; cf. section 2.4.1).

6.1.3 Headache Characteristics after Surgery

In the follow-up sample of 68 patients, 39.7% reported headache within the last three months before the follow-up investigation. Again, all different headache types were present with migraine being most common. Notably, the percentage of patients with chronic headache was reduced compared to the baseline sample. There was no or only mild disability due to headache in 70% of the patients and moderate or severe in 30%. Mixed headache locations with no clear distribution patterns were most frequently observed after surgery. The percentage of patients with frontally located headache was much lower than in the baseline sample. Thus, in our study, headache characteristics after surgery matched the heterogeneous picture before surgery. Comparative data from the literature do not exist, since, to our knowledge, this is the first study that investigated headache characteristics of patients with TSR after surgery in detail.

6.1.4 The Treatment Effect of Neurosurgery on Headache

While the description of the headache characteristics after neurosurgery suggested that there might have been an improvement of headache compared to baseline, this impression was not confirmed in the inferential statistics. 50% of the patients who had headache before surgery were without headache after surgery, but 30% of those patients without headache before surgery developed a new headache after neurosurgery. Thus, the treatment effect of neurosurgery on headache was not significant. Hypothesis 4a of the present study, stating that neurosurgery would significantly reduce the occurrence of headache in patients with TSR, therefore has to be rejected. Regarding disability due to headache after surgery, 8 patients reported an average increase in disability by 45 points in the MIDAS Score. On the other hand, 15 patients reported a reduction of disability after surgery averaging 50 points on the MIDAS Score. However, the difference of the mean MIDAS Score between t1 and t2 did not reach significance in the parametric or the non-
parametric test. Thus, hypothesis 4b, that disability due to headache would be reduced by neurosurgery, must be rejected as well.

With a remission rate of 50%, the treatment response of headache to neurosurgery in the present sample of patients with TSR was comparable to that observed by Levy (Levy et al., 2005) and considerably lower than the treatment response of 70% observed by Wolf (Wolf et al., 2016). With 30% of the patients suffering from a new headache after the operation, de novo occurrence of headache post-surgery was twice as frequent as in Levy’s sample (Levy et al., 2005). The comparison between remission rate and new occurrence rate in the present study suggests that the effect of neurosurgery is not significantly higher than the natural fluctuation of headache in patients with TSR. The observed improvement thus cannot necessarily be attributed to a treatment effect.

Together with the finding that disability due to headache could not be substantially reduced through neurosurgery, the present results fit in well with the outcome of the Norwegian retrospective cohort study conducted by Gravdahl et al. They found the improvement rate in patients who had undergone surgery to be equally high as in patients not operated upon (Gravdahl et al., 2016). While the evaluation of treatment results was not the main interest of this thesis, these results are nevertheless of relevance for clinical practice (cf. section 6.3.2).

6.2 Psychological influencing Factors of Headache in Patients with TSR

The main objective of the present thesis was the investigation of psychological factors from a proposed biopsychosocial explanatory model for headache in patients with TSR. The following sections discuss in detail the influence of personality traits, stress coping strategies and pain catastrophizing observed in the study sample and integrate the results into previous knowledge. Section 6.2.4 concludes the discussion of influencing factors with a summary of the implications for the biopsychosocial model.

6.2.1 Personality

6.2.1.1 Summary of Results

Conscientiousness and neuroticism were predictors for headache occurrence in the logistic regression model, however the relation was a very small one. It became statistically significant only with a liberal inclusion criterion and did not explain a substantial amount of variance. Parameter estimates revealed conscientiousness to be the more important predictor of both. But still it accounted only for a minimal increase in the risk for occurrence of headache. Nevertheless, the
results allow a cautious confirmation of hypothesis 1a, that personality is indeed a predictor of headache occurrence, albeit a weak one.

Disability due to headache was predicted by neuroticism with a moderate amount of variance explained. Parameter estimates demonstrated that higher values of neuroticism resulted in a slightly higher risk of moderate/severe disability due to headache. Hypothesis 1b, stating that personality would be a predictor of disability due to headache, is, thereby, confirmed.

Among the investigated personality factors extraversion and to some extent agreeableness were positively correlated to change in the MIDAS score. The more extraverted and agreeable patients were, the better they responded to neurosurgery as headache treatment. Neuroticism, on the other hand, was correlated negatively to change in the MIDAS score. This indicates that a lower neuroticism score resulted in a better treatment response of headache to neurosurgery. Thus, hypothesis 5a, which concerned the relation between personality and treatment response, can be retained.

6.2.1.2 Neuroticism

It did not come unexpected that neuroticism played a causal role in the occurrence of headache and experienced disability due to headache in the present sample of patients with TSR. It also had a negative effect on the treatment response of headache to neurosurgery. Neuroticism is the most widely investigated personality factor related to primary headache and has been consistently found to influence it (cf. section 2.5.1.1). The present results suggest that neuroticism plays a similar role as a risk factor for headache in patients with TSR as in patients with primary headache. With an odds ratio of 1.064 its influence on headache occurrence was rather small. It was, however, comparable to that found in the prediction of migraine occurrence in a study by Ishii et al., who found an odds ratio of 1.099 for neuroticism in a similar study design (Ishii et al., 2012). With an odds ratio of 1.179, neuroticism’s effect on disability due to headache in the present study was somewhat higher. This result is in line with the general observation that, consistently throughout this study, the influence of psychological factors was higher on the subjective rating of disability due to headache than the occurrence of headache.

The reason for the relation between neuroticism and headache in patients with TSR remains speculative at this point of time. While several explanations are conceivable, none of them has sufficient scientific support as of yet. It is often claimed, that emotional fragility and a tendency for negative feelings destabilizes a person and poses a general health risk. The risk for disabling
headache in neurotic patients with TSR may, accordingly, be directly caused by an increased vulnerability toward painful experiences. However, it is also possible, that neurotic patients actually experience the same amount of pain as others, but are prone to express their pain in a stronger fashion. Both possibilities are discussed in the literature on primary headache (e.g. Aaseth et al., 2011). Which one of them applies to patients with TSR awaits further investigation, though.

A third explanation, that neuroticism and a vulnerability for headache might share common predisposing factors, as for example early childhood trauma or a genetic predisposition, is theoretically conceivable. However, such a link is as yet unsupported by the literature and might in fact be difficult to prove scientifically.

There is also the possibility of reversed causality, meaning that, contrary to the presented hypothesis, increased neuroticism is the consequence of experiencing intense pain. What goes against such a line of argumentation is, that neuroticism is known to be a fairly stable personality factor. Headache in patients with TSR, in contrast, fluctuated greatly even over the course of weeks in the present study sample. It seems improbable that fluctuating pain might be able to significantly alter personality traits\(^{13}\). There is, thus, good reason to conclude that neuroticism indeed poses a risk factor for headache in patients with TSR.

The result that neuroticism is negatively related to the development of headache after surgery could be explained by neurotic patients struggling to experience or report an improvement of pain after surgery. The results have to be interpreted with care, though. Investigation of the dropouts, revealed a response bias in the follow-up sample (c.f. section 6.5.1.1). The mean neuroticism value in the dropouts was significantly higher than in those patients participating in the follow-up investigation (cf. section 3.3). This result indicates that a disproportionately high number of neurotic patients decided to discontinue the study. Thus, the variability of neuroticism in the follow-up sample was reduced and unrepresentative of the full study population. It is possible that the de facto connection between neuroticism and treatment response to neurosurgery in the full population differs from the effect observed in this sample. Since a reduced variability usually leads to a reduced power and smaller effect sizes, it is reasonable to expect the effect of neuroticism to

\(^{13}\) The possibility of a shared causal factor or reversed causality explained in this section applies in the same way for the other personality factors found to influence headache in patients with TSR. For the sake of readability they will not be repeated in each section, but should be borne in mind in the interpretation of our results.
be even bigger in the complete population. This, however, cannot be claimed with certainty without further investigation.

6.2.1.3 Conscientiousness

Conscientiousness was a weak predictor of headache occurrence in our sample, but was otherwise unrelated to headache in patients with TSR. Although conscientiousness, especially in its extremes of rigidity or obsessionality, has often been described as a defining personality trait of migraineurs, the present results are in line with a great number of empirical studies that negated a central role of conscientiousness in the development of headache (cf. section 2.5.1.1). However, the small odds ratio of 1.067 in the prediction of headache occurrence suggests a minor, but not negligible, effect of conscientiousness on headache in this study. Such an effect has not been observed in similarly designed studies on primary headache (Ishii et al., 2012).

But how can conscientiousness influence the occurrence of headache? The historically proposed explanation is that highly conscientious people tend to be tense and driven and convert their unresolved inner conflicts into pain (cf. Schmidt et al., 1986 and Naylor et al., 2017, for an overview). Although unsupported by the literature on primary headache, it cannot be excluded that inner tension in highly disciplined persons might contribute to the development of headache in patients with TSR. One could imagine that conscientious persons react to the diagnosis of TSR with higher stress and tension and, as a result, experience headache. Such a connection would most likely be mediated by muscle tension, resulting in TTH. Still, the small effect size in this study is insufficient to support a crucial role of a rigid personality in causing headache, as initially claimed by psychoanalysts.

An alternative explanation for the increased occurrence of headache in conscientious patients could be, that conscientious patients give a more accurate account of their headache. It is plausible, that conscientious patients would answer the question, whether they had had headache within the last three months, in the affirmative even if headache was slight and non-disabling. Patients with a lesser degree of conscientiousness might pass it over as unimportant and not report it at all. However, more reports of slight headaches in conscientious patients should also result in a lower average MIDAS score in this patient group. But such a difference was not evident in the present results, which argues against this explanation.
6.2.1.4 Extraversion

Extraversion has been discussed as a protective personality trait which might allow a person to better adjust to prolonged pain (Ramirez-Maestre & Esteve, 2013). In the present study, extraversion was not related to headache occurrence or disability due to headache before surgery. This is in accordance with several studies that could not confirm extraversion to be a relevant influencing factor of primary headache (e.g. Kentle, 1989, Ishii et al., 2012).

Still, an effect of extraversion on the treatment response of headache to neurosurgery was observed in this study. Extraversion was substantially correlated to a change in disability due to headache between baseline and follow-up. A possible explanation for this connection could be the ability of extraverted persons to build resilience as discussed in the literature on primary headache. Connor-Smith et al. elaborated that extraversion might supply a person with sufficient energy to initiate and persist in potentially beneficial coping strategies. Also, an outgoing nature might facilitate seeking social support. They hypothesized that extraversion would be correlated to coping-strategies of problem-solving, support seeking and accommodation and found this hypothesis confirmed in a large meta-analysis (Connor-Smith & Flachsbart, 2007). In the present intercorrelation analysis, a similar correlation pattern was found. Extraversion was most highly correlated to the coping strategies use of emotional support, active coping, use of instrumental support and planning. The correlations were of a similar size as those observed in Connor-Smith's meta-analysis (r= 0.16 to 0.19 in our sample as compared to r=0.20 to 0.25 in the meta-analysis). They failed to reach significance in the present, somewhat smaller study sample, though (cf. Table B1 in the appendix).

While these findings are in line with Connor-Smith’s results and support the idea, that extraversion facilitates beneficial coping strategies, a discrepancy with the present results remains. The coping strategies related to extraversion were not correlated to treatment response in this study. It is, therefore, suggested that a more general, positive effect of extraversion might be at work. Extraversion might lend energy to stress coping efforts irrespective of which coping strategy is chosen and thus might render stress coping more effective in general.

However, the correlation results from the follow-up sample regarding extraversion must be interpreted with caution. The analysis of the dropouts revealed a response bias, resulting in lower mean extraversion in participants than in dropouts. This is of relevance, since a systematic exclusion of highly extraverted patients can result in reduced variability in the correlation analysis. Limited variability can bias the results, but usually leads to lower correlation coefficients. It is thus unlikely,
that the observed correlation effect of extraversion and treatment response is merely a statistical artifact. On the contrary, the observed effect can be expected to be even more pronounced in the full study population. Still, the investigated follow-up sample is not entirely representative of the study population regarding their extraversion values and a statistical bias cannot be excluded (cf. section 6.5.1.1 for a discussion of the response bias).

6.2.1.5 Unrelated Personality Traits

Agreeableness. Agreeableness was not significantly associated with headache in patients with TSR. However, its correlation to treatment response was not insubstantial and only barely failed to reach significance. Higher agreeableness was correlated to a more pronounced change in disability due to headache between baseline and follow-up, which was unexpected. Agreeableness has only ever been discussed as an aggravating factor of headache with the argument that repressing hostility increases headache (e.g. Bag et al., 2005). At best, agreeableness has been found to be unrelated to headache occurrence or pain severity (e.g. Ishii et al., 2012, Chan & Consedine, 2014). But up to now, no study gave evidence of a positive effect of agreeableness on primary headache. This may well be due to the fact, that no study investigating agreeableness in association with headache included treatment response as a criterion variable, though.

The beneficial effect of agreeableness on headache after surgery observed in the present study could be explained by a more harmonious patient-doctor relationship. Agreeable patients might cooperate better with their doctors and thus achieve better treatment results. Social desirability could be another explanation. Agreeable patients could feign a treatment response to please the investigator (cf. section 6.5.1.1 for a discussion of a possible social desirability bias). However, this result was not significant and it should be interpreted with due reserve.

Openness to Experience. Openness to experience has been found to be a protective factor in primary headache in that it allows patients to react flexibly to pain. It was found to be a predictor of lower pain severity (Schmidt et al., 2011) and the impact of headache on daily life (Chan & Consedine, 2014). It was, therefore, expected to observe a positive effect of openness to experience on disability due to headache in the present sample of patients with TSR. However, openness to experience was entirely unrelated to the MIDAS score, as well as to headache occurrence and treatment response. Thus, the present results do not support the positive role of openness to experience proposed in the literature.
6.2.1.6 Conclusion on the Influence of Personality on Headache

In summary, the present results support the theory, that headache in patients with TSR is not caused by a purely pathophysiological mechanism, but is indeed influenced by the personality of the patient. In the present sample, neurotic and conscientious patients with TSR were more likely to experience severe and disabling headache, whereas extraverted and less neurotic patients had a better chance of treatment success of neurosurgery on headache. The rather small proportion of variance explained by personality was expected, since it is only one of several psychological, biological and social factors that can influence headache in patients with TSR.

As stated in the discussion of the individual personality traits, the exact mechanisms by which personality influences headache in conjunction with TSR are at this point of time still unresolved. One can only speculate that its effect is somehow mediated by stress or pain coping or by a patient’s ability to build cooperative relationships. Further research is needed to elucidate this topic.

6.2.2 Stress Coping

6.2.2.1 Summary of Results

Substance use, positive reframing, denial, humor, behavioral disengagement and self-blame were investigated as possible predictors of headache occurrence in a regression model together with pain catastrophizing. None of the investigated coping strategies was retained as a predictive factor in the logistic regression model. Although substance use and positive reframing individually correlated with headache occurrence, they did not have predictive value exceeding that of pain catastrophizing alone. Thus, hypothesis 2a, that stress coping is a relevant predictor of headache occurrence must be rejected.

In the prediction of disability due to headache, humor was found to be a significant influencing factor. It substantially increased the amount of variance explained compared to a regression model with pain catastrophizing as the sole predictor. Parameter estimates confirmed that more use of humor as a coping strategy significantly increased the risk of suffering from moderate/severe disability due to headache. Positive reframing and substance use, again, correlated with disability due to headache, but had no additional predictive value. Hypothesis 2b, that stress coping is a significant predictor of disability due to headache, is thus confirmed.
Behavioral disengagement and humor were the only two stress coping strategies, which were related to treatment response. The more these coping strategies were used by the patients, the less their disability due to headache improved. Hypothesis 5b can, therefore, be retained as well.

6.2.2.2 Humor

Humor as a coping strategy has been included into the present analysis not because it was backed by the literature as an influencing factor on primary headache, but because it was related to the outcome variables in the preliminary data analyses. In a strictly deductive generation of hypotheses, there would have been very little reason to include humor as a possible predictor, since several studies negate any effect of humor on primary headache (e.g. Lucas et al., 2007, Chan & Consedine, 2014). However, an exploratory study design, as used in the present study, allows the consideration of any variable that could possibly be related to headache in patients with TSR.

Indeed, humor was found to be a significant predictor of disability due to headache in the final regression model. Interestingly, it had a negative influence on headache and increased the risk of suffering from severe disability. More frequent use of humor as a coping strategy was also correlated to less change in disability due to headache between baseline and follow-up. This is in contrast to the many health benefits that have been attributed to humor in the literature so far (cf. Martin, 2001, for an overview).

An explanation for these, at first glance, surprising negative effects of humor observed in the present study, might be found in the variety of different types of humor, that can be adopted by patients (cf. section 2.5.2.1). Martin differentiates between benign kinds of humor (i.e. affiliative humor and self-enhancing humor) and injurious types of humor (i.e. aggressive humor and self-defeating humor; Martin et al., 2003). Since the items of the BriefCOPE that query about humor are phrased in a very general way, there remains an uncertainty about the patients’ interpretation of the respective questions (cf. section 6.5.3. for a discussion of the choice of questionnaires). When asked if they “made fun of the situation frequently”, it is conceivable, that they could have thought of derisive or self-disparaging remarks, which would explain the deleterious effect on disability and treatment response. When inspecting the correlation of humor to personality traits, humor was related to low agreeableness. This could be a hint that indeed the aggressive types of humor prevailed in the present study. At present, this remains only a theory, though. A further investigation of humor and its effect on headache with the help of an inventory, which is able to distinguish between the different humor types (e.g. the Humor Styles questionnaire; Martin et al., 2003) would be of great interest.
Finally, reversed causality is another potential explanation. Perhaps, patients who suffer from severe, disabling pain, that is refractory to therapy, might revert to humor as an accommodation strategy to adjust to the uncontrollable situation. Also, a shared cause of headache and humor as a coping strategy is a theoretical option, although no plausible common factor comes immediately to mind.

6.2.2.3 Behavioral Disengagement

Behavioral disengagement in the sense of completely avoiding dealing with stressful situations is a coping strategy, which has provoked a controversial debate in the field of primary headache research. It can be understood as a form of stress avoidance, which is commonly believed to be effective in preventing headache attacks. In recent years, however, it has been pointed out, that stress avoidance might be stressful in itself and pose a health risk. A harmful effect might be expected especially, if behavioral disengagement is understood less as a conscious choice to manage headache triggers, but more as a resigned passivity resulting from hopelessness (cf. section 2.5.2.1).

In the present study on patients with TSR, behavioral disengagement was unrelated to headache occurrence and disability due to headache. In the investigated patients with TSR, there was, thus, no evidence for a positive effect of behavioral disengagement as has been observed in migraine patients (Chan & Consedine, 2014). On the other hand, we found behavioral disengagement to be highly negatively correlated to treatment response. Patients who had higher values of behavioral disengagement experienced a lesser change in disability due to headache between baseline and follow-up. Lucas et al. obtained similar results concerning treatment response to medication in migraine patients. In their study, combined scores of denial and behavioral disengagement were significantly higher in non-respondent patients (Lucas et al., 2007).

What could be the reason for this observed negative effect? It has to be noted, that the phrasing of the behavioral disengagement items in the BriefCOPE (“I've been giving up trying to deal with it.”, “I've been giving up the attempt to cope”) are focused on the aspect of “giving up” and may thus appeal to hopeless or depressed patients. One could assume that these patients lack confidence in their treatment and tend to experience treatment results in a negative way. Arguing against this
theory, however, is that in fact behavioral disengagement did not correlate with depression as measured in the PHQ9 at all ($r=0.070$, ns., analysis not shown in the results\textsuperscript{14}).

Perhaps, patients did not disengage out of depressiveness but as a conscious choice to avoid stress. Still, this did not result in reduced disability as in migraine patients, but rather in an insufficient treatment response. One can speculate, that patients suffering from migraine, which is known to be frequently triggered by stress, profit more from stress avoidance than patients with a TSR, which requires vigorous commitment to therapeutic measures. It has to be left open for further research to elucidate whether patients, who use the coping strategy of behavioral disengagement frequently, indeed lack therapy commitment.

A reversed causality, in that lack of treatment response causes behavioral disengagement, can be excluded here, since coping strategies were queried prior to treatment. That a history of chronic headache is the common cause for both, patients to disengage and neurosurgery to insufficiently relieve headache, seems feasible, though. However, it would then be reasonable to expect behavioral disengagement to be related to disability due to headache before surgery as well.

### 6.2.2.4 Substance Use

The use of alcohol or drugs as a means of coping with stress correlated negatively with headache occurrence and disability due to headache. It was of no additional predictive value, though, and was not retained in the final regression models. Substance use can thus be understood as an influencing factor of minor importance on headache in patients with TSR.

At first glance, the direction of the correlation is surprising. Patients with less substance use tended to have headache more frequently and had a higher disability due to headache. Since alcohol consumption is a common headache trigger and has been found to be a significant predictor of disability due to headache in migraineurs (Chan & Consedine, 2014), it would have been expected to have a negative influence on headache in patients with TSR as well. Most likely though, the observed effect can be explained vice versa: the ability of alcohol to induce headache is publicly well-known and Dueland observed, that headache patients tend to abstain from alcohol in order to prevent further pain attacks (Dueland, 2015). Quite possibly, the investigated patients with TSR and

\textsuperscript{14} Data for this additional analysis were kindly provided by R. Carneiro Scholl, who investigated depression via the Patient Health Questionnaire-9 (PHQ9) in the same sample for her own dissertation.
severe headache acted in the same way and, thus, used alcohol for stress relief less frequently than patients with no or only slight headache.

Another explanation could be, that patients thought of analgesics, when answering about substance use, which could certainly cause decreased headache occurrence and disability due to headache. But since the German translation of “alcohol and drugs” reads “Alkohol und Drogen”, and that the latter in common usage refers to illegal drugs only rather than to medication, this theory seems unlikely. There neither appears to be an obvious common cause for headache and reduced substance use. Nevertheless, the possibility of a shared cause should be kept in mind as an alternative explanation.

6.2.2.5 Positive Reframing

Just like humor, positive reframing has been added to the regression models because of apparent correlations to the outcome variables in the preliminary data analyses, rather than for its unambiguous association with primary headache. Its successful use in CBT for headache treatment suggests that it influences headache in a positive way, though (cf. section 2.5.2.1).

In our main analysis, positive reframing remained substantially correlated to headache occurrence and disability due to headache. But it was not able to explain any additional variation in the regression models and was, therefore, not retained as a predictive factor. So, it is considered a minor influencing factor of headache in patients with TSR. But in stark contrast to its good reputation, positive reframing in our study was related to more frequent headache and more severe disability due to headache. This result differs largely from studies in primary headache, which, in general, find positive reframing either to be irrelevant (e.g. Massey et al., 2009, Chan & Consedine, 2014) or positive (Holroyd et al., 1977, Lucas et al., 2007).

In search for an explanation, it must be kept in mind, that a specific coping strategy is never uniformly adaptive or maladaptive, but its usefulness is dependent on the specific situation and person using it (cf. 2.5.2). Thus, even positive reframing, which seems to be of universal good use in CBT not only with headache but a variety of psychiatric diseases, might be maladaptive under certain conditions. For example, finding a positive view on the situation might prevent further attempts of the patients to actually change the situation. Also, the aim of CBT is usually not pain reduction but the improvement of QoL in the face of recurrent pain. By analogy, it is possible, that instead of reducing pain perception or the impact of headache on daily living, positive reframing
helped the patients studied here, to enhance their psychological wellbeing, which was not investigated in this study.

Even so, the fact that the present study is the only one which found a negative influence of positive reframing on headache occurrence and disability due to headache, amidst a multitude of studies attesting this coping strategy to be beneficial or irrelevant, remains curious. Considering a possible reversed causality or a shared cause of headache and positive reframing also yields no further insights. It has to be conceded, this result cannot be explained satisfactorily, at present.

6.2.2.6 Unrelated Stress Coping Strategies

Denial. Denial has been found to be frequent in patients with primary headache (Hassinger et al., 1999, Lopez-Lopez et al., 2017). It appears to be involved in headache chronification (Marlowe, 1998) and is associated with lack of treatment response (Lucas et al., 2007). It was, therefore, hypothesized that denial would have a negative influence on headache in patients with TSR. However, in the present study denial was entirely unrelated to headache occurrence, disability due to headache and treatment response.

Self-Blame. Self-Blame is an established predictor of primary headache disorders in adolescents (Kröner-Herwig & Gassmann, 2012), and was expected to be a predictor of headache occurrence in patients with TSR. On the contrary, it did not significantly influence headache in patients with TSR, which went against the hypothesis of this study. However, while its correlation to headache occurrence was insubstantial, correlation to disability due to headache (r=0.231, p=0.055) and change in disability due to headache (r=-0.256, p=0.116) only barely failed to reach significance. Thus, self-blame should not entirely be ruled out as a potential influencing factor of headache in patients with TSR. The relation between self-blame, depression and headache in patients with TSR should be further investigated in studies with larger sample sizes.

6.2.2.7 Conclusion on the Influence of Stress Coping

The present results indicate a considerable influence of stress coping on headache in the population of patients with TSR. They particularly support the importance of humor and behavioral disengagement. Accordingly, patients with TSR who use humor as a coping strategy tend to experience more disabling pain and a lesser treatment response. The results equally imply, that patients disengaging from stressful situations benefit less from neurosurgery with respect to headache relief. A minor influencing effect of positive reframing and substance use on headache in patients with TSR is also supported by this study.
Interestingly, the stress coping strategies found to be of influence on headache in patients with TSR all belong in only two of the core categories suggested by Skinner’s stress coping model. Behavioral avoidance and substance use belong in the core category of escape. They, thus, serve the purpose of exiting a noncontingent environment. Positive reframing and humor are accommodation strategies and as such are adjustments of the patient’s preferences to the available options. It makes sense that escape and accommodation strategies should be of relevance to this patient group, since a tumor diagnosis is an uncontrollable event and cannot be prevented. At least shortly after receiving the diagnosis, escape or cognitive adjustment may seem to be the only strategies available. But since good treatment options for TSR exist, the initial stress of the diagnosis might be relieved for those patients using more active coping strategies. Escape and accommodation on the other hand could even perpetuate the stressful experience and, thus, increase the risk for severe headache.

The results on coping strategies cannot easily be transferred to individual patients, though. For example: while humor is detrimental for the majority of the present study group, it is not necessarily detrimental for all patients with TSR. As explained before, adaptive stress coping is a highly individual process (cf. section 2.5.2). So, the present results do not allow any counsel on which coping strategy to use in a specific situation. They should rather be interpreted as evidence of the principle that stress coping has an influence on headache in patients with TSR at all. This argues further against a purely pathophysiological explanatory model.

6.2.3 Pain Catastrophizing

6.2.3.1 Summary of Results

Pain Catastrophizing was retained as the only predictor of headache occurrence in the combined stress coping/pain catastrophizing logistic regression model. The amount of variance explained was small, though. Parameter estimates indicated that higher pain catastrophizing increased the risk of headache occurrence only minimally. Despite the small effect size, the results confirm hypothesis 3a, that pain catastrophizing is a significant predictor of headache occurrence.

Pain catastrophizing was the most relevant predictor in the combined stress coping/pain catastrophizing logistic regression model for the prediction of disability due to headache. It added substantially to the amount of explained variance and increased the percentage of correctly classified cases. Parameter estimates confirmed that higher pain catastrophizing significantly
increased the risk of suffering from moderate/severe headache. Thus, hypothesis 3b, that pain catastrophizing predicts disability due to headache, is confirmed.

Unexpectedly, pain catastrophizing was not significantly related to change in the MIDAS Score between baseline and follow-up. The respective hypothesis 5c, that pain catastrophizing correlates to treatment response, must therefore be rejected.

6.2.3.2 The Role of Pain Catastrophizing

The present results suggest that pain catastrophizing predicts headache in patients with TSR as reliably as it predicts primary headache. Drahovzal et al. found pain catastrophizing to be a significant predictor of weekly headache, which was able to explain a small amount of variance (Drahovzal et al., 2006). This is similar to the present result in the prediction of headache occurrence in patients with TSR. With a Nagelkerke $R^2_{\text{MAX}}$ of 0.090, the amount of explained variance was close to the $R^2$ in Drahovzals study (combined $R^2$ for anxiety sensitivity and pain catastrophizing = 0.050).

The influence of pain catastrophizing on disability due to headache was considerably higher. This is in line with several studies finding it to be a significant predictor of pain intensity, impact on daily living and disability in primary headache (Holroyd et al., 2007, Buenaver et al., 2008, Kröner-Herwig & Maas, 2013). Surprisingly though, pain catastrophizing was not related to a change in disability due to headache between baseline and follow-up. Treatment response of headache to neurosurgery was, therefore, unrelated to pain catastrophizing in patients with TSR.

But why was pain catastrophizing that detrimental to patients with TSR? Previous studies have investigated various mechanisms in which pain catastrophizing can modify pain in general (cf. section 2.5.3). It has been discussed, that patients with high pain catastrophizing may experience an attentional shift towards pain perception and thus experience pain more severely (Crombez et al., 1998, Sullivan et al., 2001). Bandura suggested, that an inhibited emission of endogenous opiates associated to pain catastrophizing could also be involved in the increased perception of pain (Bandura et al., 1987). It is reasonable to assume, that these same mechanisms are involved in the development of headache in patients with TSR as well. Patients, who tend to have pain catastrophizing thoughts, may interpret headache as a symptom of the tumor. As such, it would be appraised as a direct threat and require an attentional shift towards the threatening information, i.e. the headache. This may cause an increased pain sensitivity and even an inhibited emission of endogenous opiates. As a result, patients with TSR and a tendency for pain catastrophizing would perceive headache as more frequent and more disabling.
It is also possible that the repeated exposure to severe headache facilitates catastrophizing thoughts. A history of chronic pain might cause more severe headache and pain catastrophizing at the same time. Though Sullivan claimed that pain catastrophizing remains fairly stable over time (Sullivan et al., 2001), this has only been investigated over the course of months (Sullivan et al., 1995). However, many patients with TSR have a history of headache going on for years. It is conceivable that they might engage in a vicious cycle, in which severe pain experience causes pain catastrophizing and pain catastrophizing causes increased headache severity. This mechanism could lead towards chronification. At any rate, this could only be confirmed in a longitudinal study design and repeated measurements of pain catastrophizing.

Additionally, Sullivan’s observation, that patients with pain catastrophizing express their pain more freely is of special interest with regard to the present study. Sullivan argued that the open expression of pain might be helpful in eliciting support but could intensify pain through the prolonged mental occupation with its bothersome quality (Sullivan et al., 2000). In the present clinical sample of patients with TSR, 24% of the patients received tumor diagnosis based on MRI scans performed due to serious headache. It is conceivable, that those patients who tend to catastrophize painful experiences, would interpret their headache as a sign of a dangerous illness and express this fear towards their doctor. They would, thus, be more likely to receive an MRI due to headache. In correspondence with this idea, pain catastrophizing was significantly higher in those patients receiving MRI due to headache than in all other patients (post hoc analysis, cf. Table B2 in the appendix).

Sullivan also hypothesized, that an exaggerated expression of pain could prompt health care professionals to instigate more invasive treatment efforts (Sullivan et al., 2001). It would be interesting to find out, if the physician’s treatment decision for neurosurgery of TSR was influenced by the patient’s catastrophizing thoughts and pain expression. In the present study no data on the physician’s reason for this treatment decision were collected. Treatment response with regard to headache was investigated and found to be unrelated to pain catastrophizing, though. So, even if the physician’s decision to operate on the tumor was biased, it did not lead to worse treatment results regarding headache for pain catastrophizing patients than for others.

6.2.3.3 Conclusion on the Influence of Pain Catastrophizing

The present results underline the importance of pain catastrophizing as an influencing factor of headache in patients with TSR. Accordingly, disability due to headache can be particularly aggravated by it, while treatment response seems to be largely unaffected. This is on the one hand
interesting, because it lends further support to the biopsychosocial explanatory model. Moreover, it is of some interest for clinical practice, since it is likely that pain catastrophizing and its associated pain behavior can have an impact on the diagnostic process and course of treatment (cf. section 6.3.3).

### 6.2.4 Summary of the Biopsychosocial Explanatory Model

Considering the observed influence of personality traits, stress coping strategies and pain catastrophizing in this study as a whole, there is substantial evidence for a psychological component in the causation of headache in patients with TSR. Headache occurrence as well as the experienced disability due to headache and treatment response of headache to neurosurgery can no longer be understood as mere consequences of the mechanical and biochemical properties of the tumor. Instead, the present study suggests, that a complex interaction of biological, psychological and situational aspects determines the experience of headache in patients with TSR.

The exact mechanisms, by which psychological factors are able to influence the perception of pain in patients with TSR, are, at present, still largely speculative, though. The results from the present study allow for the formulation of the following theory of biopsychosocial interaction:

It is suggested, that the diagnosis of TSR can be perceived as a major stressful life event, as is known to be associated with an increased risk for headache (De Benedittis et al., 1990) A patient’s ability to cope with stress successfully will modify the subjectively perceived stress level and the associated health risk. Which coping strategies patients choose, and how much energy they are able to invest in stress coping, will in turn be influenced by their respective personality. When a patient first experiences unpleasant sensations in association with TSR, pain catastrophizing will supposedly gain importance as an aggravating factor. A patient with a great amount of pain catastrophizing will interpret even ambiguous sensations as potentially threatening and attributable to the tumor. Thoughts of being helplessly subjected to pain and unable to deal with this sensation, will increase the bothersome quality of the headache. The patient’s attention will inadvertently shift to all putative symptoms of a dangerous exacerbation of the tumor, i.e. headache. It is suggested, that the catastrophizing thought can amplify the experienced headache sensation by inhibiting the emission of endogenous opiates. As a consequence, patients can get caught in a vicious cycle in which pain catastrophizing thoughts and severe pain perceptions intensify each other.
The proposed biopsychosocial explanatory model also implies an influence of psychological factors on the patient’s treatment response to neurosurgery with regard to headache. Based on the present results, it can be hypothesized that extraverted and agreeable patients will benefit from their ability to form cooperative patient-doctor relationships. In contrast, a tendency for coping strategies of escape and accommodation will supposedly harm a patient’s commitment to therapy and result in a reduced treatment response.

While this theory of a biopsychosocial causation of headache in patients with TSR is in concordance with the present exploratory results, it certainly needs further confirmation. A number of questions for further research arise from the suggested interactions between medical and psychological factors. These will be discussed in section 6.4.

6.3 Implications for Clinical Practice

6.3.1 Diagnosis of Headache directly attributed to Tumors of the Sellar Region

With every patient presenting to a health care professional with TSR and headache, there is the open question, whether the TSR is directly responsible for the occurrence of headache. The diagnosis of headache directly attributed to intracranial neoplasms requires evidence of causation, either by a development of headache in temporal relation to the tumor, a worsening in parallel with the tumor or by an improvement of headache after surgery (cf. section 2.1.1).

Following these diagnostic criteria, it could be helpful for the physician to investigate the temporal connection of headache with the emergence of TSR. However, it is impossible to know how long the TSR had remained undetected prior to diagnosis and whether headache started in close temporal proximity or worsened in parallel with the tumor. Thus, even an exact medical history of headache is probably insufficient to make a reliable diagnosis of headache attributed to TSR before surgery.

Improvement after surgery is, thus, the only evidence of causation that can be proven with certainty. However, the physician must make a diagnosis before surgery to decide on an appropriate treatment strategy. But are there any characteristics of headache, that allow the physician to decide beforehand, whether headache is related to TSR and thus decide, which headache will recede after neurosurgery?
When integrating the results of the present thesis into current scientific knowledge, the following clinical picture of headache in patients with TSR can be drawn: Patients with TSR can present with all different headache types and severities, episodic or chronic headache, different amounts of disability due to headache, heterogeneous headache locations, new onset or long-standing headache and varying durations and frequencies of pain attacks (cf. sections 2.4.1, 4.1, 6.1.2). As of yet, there is no evidence that any of these characteristics can be used to predict which patient will benefit from neurosurgery and which will not. It is thus impossible for the treating physician to deduce from the patient’s presenting symptoms whether the headache can be attributed to TSR before surgery has taken place.

Also, a correct diagnosis of headache attributed to TSR cannot be derived from the clinical characteristics of the tumor. Many influencing factors have been discussed as possible pathophysiological causes. But neither tumor size nor intrasellar pressure, nor hormonal hypersecretion are reliably linked to the development of headache in patients with TSR (cf. section 2.4.2). These factors cannot predict improvement of headache after neurosurgery, either (cf. section 2.4.3). The physician diagnosing and treating headache in patients with TSR, thus, receives no reliable clue pointing to headache attributed to TSR from the presentation of the tumor characteristics.

It is, in summary, entirely possible, that there is a subgroup of patients, whose headache is directly attributable to the tumor. At this point of time, it is, however, impossible to identify them reliably, especially not prior to surgery. At any rate, in the present study only 19% of all patients with TSR suffered from headache that improved significantly after neurosurgery (cf. section 5.2.2 and section 6.1.1). Even that treatment response could at least in part be attributable to psychological rather than biological factors (cf. sections 6.2.1.4, 6.2.2.2 and 6.2.2.3). It can, therefore, be concluded, that the subgroup of patients with headache caused solely by TSR must be considerably smaller than suggested by previous studies.

On the other hand, the absence of a direct pathophysiological cause does not imply that headache must be entirely unrelated to TSR. As explained in section 6.2.4, headache could indirectly be caused by the TSR, by example through the stress elicited by the tumor diagnosis. But headache in patients with TSR was, in the present study, clearly associated with similar psychological risk factors as primary headache. It can be concluded, that at least some proportion of the observed headache was primary headache, merely coinciding with the diagnosis of TSR. Unfortunately, this study, as others before, was unable to detect any defining features, which would help to distinguish the three
headache types from each other: headache directly attributed to TSR, headache indirectly attributed to TSR and primary headache entirely unrelated to TSR. The differential diagnosis of these headache types will, thus, remain a diagnostic challenge and must, for now, remain more or less indistinct.

6.3.2 Neurosurgery as a Treatment Option for Headache in Patients with TSR

The results of this study strongly support the recommendation voiced by Evans and Levy in 2008, that neurosurgery should only be performed on patients with TSR with sufficient indication apart from headache, but never on the basis of headache alone.

The treatment results of neurosurgery on headache in patients with TSR in this study were entirely unconvincing. While 50% of the patients with headache experienced headache relief, the 30% rate of new headache in patients previously not afflicted (cf. section 5.2.1), clearly suggests that a considerable amount of treatment success is merely due to the natural fluctuation of headache in patients with TSR.

And what is more, the treatment success in the present sample was substantially related to personality and stress coping (cf. sections 5.3 and 5.4). Thus, some share of the treatment effect was probably not caused by the removal of a pathophysiological cause, but by the patient’s own psychological reaction to treatment. Quite possibly, similar positive effects could be evoked by less invasive forms of headache treatment.

Considering also the ambiguous diagnosis of headache attributed to TSR (cf. section 6.3.1) and the lack of reliable clinical predictors for treatment success (cf. section 2.4.3), neurosurgery seems to be an unsuitable treatment choice alone for the symptom of headache in patients with TSR. If surgery is not indicated for other reasons, alternative therapy options to treat the headache should be considered (cf. section 6.3.4).

6.3.3 Considering psychological Factors in day-to-day Practice

Health care professionals involved in the treatment of headache in patients with TSR should be aware of the psychological factors influencing headache perception and pain behavior. For one, there is a need to acknowledge that headache is not necessarily caused by biological factors alone, but can be triggered or aggravated by psychological factors, even when a tumor seems to be the obvious cause. It is, admittedly, unreasonable to expect a physician to understand, take into account and possibly deal with all the psychological aspects of headache during the short course of
a doctor’s visit. But empathetic attention to psychological topics and a willingness to call in a psychotherapist, if necessary, would certainly be of help.

Furthermore, the results of the present study should serve to view the diagnostic and therapeutic decision-making process of headache in the context of the diagnosis of a TSR with caution. The results from the present thesis suggest, that severe headache and pain catastrophizing are interconnected in patients with TSR. Moreover, it is known from previous research, that pain catastrophizing is linked to pain behavior. Pain catastrophizing patients are more likely to use health care resources and are probably able to elicit offers of assistance in their social surroundings by amplified expression of pain (cf. sections 2.5.3, 4.3 and 6.2.3.2). This can be locally adaptive and result in a higher level of instrumental support. However, it involves the danger that some patients with primary headache receive a diagnostic MRI due to their aggravated expression of pain upon which an incidentaloma appears. Further, considering their apparent state of pain it might be decided to perform an otherwise unnecessary invasive procedure such as surgical tumor removal.

Thus, health care professionals should be aware that expression of intense pain is not in all cases a sign of a more severe biological cause, but can be enforced by the patient’s catastrophizing thoughts. Of course, such obvious suffering warrants an empathetic response and the offering of helpful health care services. But the physician has to keep in mind that such patients will not necessarily benefit from invasive therapies like neurosurgery. In fact, pain catastrophizing was entirely unrelated to treatment response to neurosurgery in the present sample (cf. section 6.2.3). Instead, interdisciplinary treatment approaches could be of help, since it is known that pain catastrophizing can be reduced in cognitive trainings (Thorn et al., 2007).

6.3.4 Interdisciplinary Treatment Approaches

Considering the biopsychosocial explanatory model, it seems plausible, that patients with TSR and headache would benefit from an interdisciplinary treatment, which combines medical, physical and psychosocial interventions. To our knowledge, there are, as yet, no specialized treatment groups for patients with TSR. There are, however, interdisciplinary treatment concepts for patients with primary headache, which might work equally well for patients with TSR. Scharff, for example, described convincing treatment results of an interdisciplinary outpatient group treatment in patients with intractable headache (Scharff & Marcus, 1994).

The data from the present study allows for the making of some suggestions as to what could be helpful in the CBT component of an integrative treatment approach for headache in patients with
TSR. For example, it could be of help for the patients to review with a psychologist, which stress coping strategies are adaptive and maladaptive to their personal situations. Also, learning cognitive techniques and pain coping skills could help improve the confidence in their ability to deal with pain and reduce pain catastrophizing thoughts. Training of interpersonal skills might help in finding ways of asking for assistance without the need for damaging pain behavior. And while personality cannot (and should not) be changed by psychotherapy, it might be useful to reflect on the strengths and drawbacks that come with each personality trait, so as to learn how to best handle them.

These are, however, only first ideas for CBT treatment resulting from an early exploratory study. Whether these factors are indeed helpful in the therapy of headache in patients with TSR must be the subject of future studies (cf. section 6.4.4).

6.4 Implications for Future Research

6.4.1 Confirmation of the Regression Models

The statistical analysis performed in this study was a stepwise regression procedure. In this approach, the order of the predictor variables retained in the regression model is independent from the researcher’s hypothesis and only determined by the size of their correlation to the criterion variable. This is a helpful procedure to explore data in the absence of precise hypotheses on the order of importance of the individual predictors, which was the case in the present study, since the matter had never been investigated before. However, since in this method, each variable gets credited only for its contribution to the amount of explained variance beyond that one of the previously entered variables, minor differences in the correlations can lead to profound differences in the apparent importance of the variables in the regression models.

Thus, the present results should be regarded as exploratory in nature and the order of importance of the predictors as provisional and pending further confirmation. The next step in the scientific investigation of these predictors would be to replicate the results in an independent sample. From the exploratory results of this study, exact hypotheses on the importance of each predictor can now be derived. The resulting model can be confirmed in a hierarchical regression, in which the order of entry is assigned by the researcher. It is recommended to take into consideration not only the highly significant factors from this study, but also the minor influencing factors like agreeableness, substance use and positive reframing, since they could well gain importance in an independent sample. Eventually, controlled clinical interventions will be necessary to confirm the causal role of
the potential influencing factors, since regressions are correlative methods and as such unable to prove causality.

6.4.2 Investigation of Hypotheses derived from the Biopsychosocial Explanatory Model

The present thesis is the first study advocating the theory of a biopsychosocial causation of headache in patients with TSR. It provides first exploratory evidence for a psychological component relevant for the explanation of headache in this patient group. It is hoped, that these first results will inspire further investigations of influencing factors beyond a purely mechanical understanding of headache with TSR. An investigation of the following research questions arising from the proposed theory of biopsychosocial interaction would be helpful in further elucidating the mechanisms causing headache in patients with TSR.

Perceived Stress Level. As suggested in section 6.2.4, the observed influence of stress coping could result from varying subjective perceptions of the stress associated with TSR. It can be imagined that the diagnosis of a tumor and the following surgical treatment constitute a major stressful life event to the patients. The present study did not include an inventory measuring the actually perceived stress levels, though. An investigation of subjective stress perception associated with the diagnosis and treatment of TSR and its potential relationship with headache would be of interest.

Patient-Doctor-Relationship. The reason, why agreeable patients tend to benefit more from neurosurgery regarding their headache could be that these patients are more able to successfully form cooperative relationships with their treating physician (cf. section 6.2.1.5). An investigation of patient-doctor interactions and their association with personality traits and treatment success could further explain the positive effect of agreeableness.

Commitment to Treatment. It was suggested in section 6.2.4 that escape and accommodation coping could be detrimental to treatment response, because these strategies keep patients from actively committing themselves to therapy. The relationship between coping strategies, commitment to therapy and treatment response could be an interesting subject for further investigation.

Interaction between Personality and Stress Coping. The present study could prove, that personality and stress coping both influence headache in patients with TSR. But since there was no joint regression model, the interaction between these factors remained unclear. Especially the beneficial effect of extraversion on treatment response could presumably be mediated by more
effective stress coping. Future studies could search for additional evidence on the association between these factors.

**Humor.** Humor as a coping strategy is too complex to be sufficiently covered by the two BriefCOPE items used in this study (cf. section 6.2.2.2 and 6.5.3). In the light of the substantial predictive role of humor in this study sample, the question, of which type of humor is employed by the patients, is worth a more profound investigation.

**Pain Behavior.** In previous studies, pain catastrophizing was found to be associated with intensified pain expression, which could potentially lead health care professionals to arrange more invasive diagnostic and therapeutic measures. It would be of interest, to find out whether pain catastrophizing and its associated pain behaviors contribute to the rising numbers of incidentalomas (and other incidental pathologies) diagnosed in MRIs, which were performed due to the report of severe headache. It could also be investigated, whether pain behavior influences the physician’s decision for neurosurgery and whether this impedes treatment success.

**Endogenous Opiates.** There is as of now only one study pointing to an association between pain catastrophizing and the emission of endogenous opiates (Bandura et al., 1987). Whether this association exists at all and whether it could be the reason for increased headache severity in pain catastrophizing patients, would be of great scientific interest.

**Further psychological Factors.** With personality, stress coping and pain catastrophizing, the present study investigated only three of the potential psychological influencing factors. These were chosen due to their apparent association with primary headache in previous studies. However, once it is acknowledged that psychology is of relevance to headache in patients with TSR, there are a multitude of other factors that could equally be of influence. Among others, self-efficacy, fear avoidance beliefs and attitude towards medication could be investigated in future studies.

**Mechanical and biochemical Factors.** The present results do not preclude a relevant mechanical or biochemical influence of the tumor on the development of headache. While the previous research on biological influencing factors is as of yet rather inconclusive (cf. section 2.4.2), it seems possible that the ignorance of potential psychological covariates, obscured an actually existing association. If future studies follow a multidimensional approach, in which biological factors are investigated alongside psychological factors, it might well lead to a clearer understanding of the mechanical and biochemical mechanisms leading to headache in patients with TSR.
**Social Factors.** The present study focused solely on psychological factors that influenced headache in patients with TSR. The biopsychosocial model suggests, however, that social factors might be of equal importance. Social support, financial situation and employment of the patients are only some of the potential social influencing factors that future studies could include.

### 6.4.3 Clarification of Prevalence

With 52.7% of the patients in the study sample reporting headache within the last three months prior to the investigation and a maximum of 19% directly attributable to TSR according to the ICHD-3 criteria, the present study found a substantially lower prevalence for headache in patients with TSR than previous studies (cf. section 6.1.1). The present results suggest that a significant amount of headache previously attributed to TSR is instead only indirectly related to the lesion found, or entirely unrelated primary headache. Future estimations of the prevalence of headache in patients with TSR should acknowledge the difficulty in diagnosing headache directly attributed to TSR and give an exact description of their diagnosing criteria.

The difference between the prevalence of headache within the last three months prior to the study and headache at the time of investigation in our sample also points at a substantial fluctuation of headache in patients with TSR, even over short time periods. Previous studies often did not state, which time frame they considered for their prevalence estimation. Future studies should report more clearly in which time span the occurrence of headache was measured (e.g. headache within the last week/the last month/the last three months prior to diagnosis of TSR). This may explain some of the variance in the prevalence estimations and provide a clearer conception of the time course of headache in patients with TSR.

### 6.4.4 Assessment of Treatment Effects

The development of more integrative treatment approaches for headache in patients with TSR can at this point of time be no more than a distant goal. While the results of the present study allow for the making of some suggestions, as to what could be helpful in therapy (cf. section 6.3.4), the results are too preliminary to actually deduce specific therapeutic recommendations. However, the mere result that there are indeed psychological influencing factors in the development of headache and the perceived disability due to headache in TSR is encouraging. If future studies invest some effort into the clarification of the causal relationship between psychological factors and headache and assess systematically whether a change in the psychological factors in fact results in reduced headache, new leverage points for the therapy of headache in patients with TSR might be found.
6.5 Limitations

6.5.1 Potential Biases

6.5.1.1 Response Bias

All patients that were admitted to the participating university hospital for first-time surgery of TSR and were willing participate were included into the study. The investigated sample is, therefore, a clinical sample, which is not guaranteed to be fully representative of the entire population of patients with TSR. It is possible, that certain personality factors, coping strategies or especially pain catastrophizing increase the probability to receive a diagnostic MRI or to be scheduled for neurosurgery. In this case, the respective influencing factor would be overrepresented in the study sample as compared to the full population.

The same is true for the follow-up sample. But in contrast to the baseline sample, it was possible here to analyze the drop-outs. The results revealed that drop-outs did not differ from participants concerning gender distribution and most of the investigated psychological factors. However, participants were significantly older, less neurotic and less extraverted than drop-outs. The investigated follow-up sample is thus not entirely representative of the complete study sample and the generalizability of the results to younger patients should be regarded with some caution. Also, the response bias may have impacted on the correlation analyses of neuroticism and extraversion, which is discussed in the respective sections (cf. sections 6.2.1.2 and 6.2.1.4).

However, the possibly limited generalizability of the results does not detract substantially from their validity. The response bias problem is shared by all studies on clinical samples and is, therefore, equally prevalent in the previously published literature. The present sample was chosen carefully to minimize the influence of the response bias to the minimum. It can, therefore, be assumed, that the observed results will prove to be robust and can be replicated in independent samples, although this must, of course, be left to future studies.

Social Desirability Bias. As every other study using self-reporting measures, the present study bears the risk, that patients might answer the questionnaires untruthfully. This could be of special importance in the evaluation of treatment effects, since patients could exaggerate treatment success to please the investigator. This would lead to an overestimation of the treatment effect. But since the treatment effect was insignificant in any way, a social desirability bias would not lead to an undue distortion of the results. Also, treatment success was assessed by means of a postal
survey and the patients were, thus, not directly confronted with the potential expectations of the investigator. It is, therefore, presumed that social desirability plays only a minor role in the present study.

### 6.5.2 Sample Sizes

The present study started out with a sample size of N=112. Taking into consideration the rareness of TSR and the sample sizes of comparable studies, this is a rather large study group, which is certainly sufficient to answer the posed research questions.

However, due to several problems during the data collection, the sample sizes of individual calculations are, in part, considerably lower. First of all, this is owed to the fact, that the study design was amended halfway through the study (cf. Figure 3 in section 3.1). Thus, 41 patients did not receive the full set of questionnaires. While this is regrettable, it could not be helped, since the investigation of psychological factors had primarily been planned as a minor sub-investigation of the larger study project. It only gained importance after preliminary analyses. The only alternative would have been to not investigate the additional questionnaires at all, which would have deprived the study of some of its significance.

A second problem in the data collection arose from the automatic execution of the computational questionnaires. The MIDAS, EHI and the headzones module where each preceded by an individual entry question (either “Did you have headache within the last three months?” or “Do you currently have headache”). Each of them was only presented to the patient, if the respective entry question had been confirmed. This is a standard setting of the painDetect software and cannot be influenced by the investigator. The finding, that patients did not necessarily give the same answer to all three entry questions, was unexpected. While 52.7% received the MIDAS questionnaire, only 40.2% filled in the EHI and 43.8% the headache module. Precisely speaking, for 14 patients who had headache within the last three months prior to the study but who reported no headache at the time of investigation, no diagnostic information about the headache type was available and for 10 patients the headache location was missing. These missing data concerned only the descriptive analyses and not the main regression analyses. Still, it is inconvenient, as the missing information would have certainly been of interest.

Finally, the response rate of 60.7% to the postal follow-up survey was only moderately high. And since not all of the 68 patients who answered the follow-up survey had filled in all the psychological
questionnaires at baseline, the sample size was further reduced. Patients did not state their reasons for dropping out of the study, so that it remains uncertain why the response rate was not higher.

The varying sample sizes have been carefully taken into account in the planning of the statistical analyses. Only procedures that were appropriate for the respective sample size were chosen. Also, for each result the underlying sample size is reported in the results section. There remains the possibility that the analyses with smaller sample sizes lack sufficient power to reveal effects of small effect size. A replication of the results in a larger sample is, hence, desirable.

6.5.3 Choice of Questionnaires

The questionnaires for the present study were carefully chosen and are mostly well validated. Still, two points for discussion arise.

The BriefCOPE questionnaire is without question the weakest of the applied questionnaires. With only two items per scale, the scales have a lower internal consistency than those of the other questionnaires and, in part, lack conceptual clarity. The BriefCOPE thus allows no in-depth insight into the psychological mechanisms of stress coping. This is especially notable in the discussion of humor as a coping strategy, where the brief cope is unable to distinguish between benign and injurious types of humor (cf. section 6.2.2.2). However, the BriefCOPE was chosen for its practicability. Since the present thesis was part of an extensive research project, it was of major importance to limit the number of questionnaire items so as to reduce the time demands for participants. For this purpose, the BriefCOPE was best suited, since it is economical and still reasonably well validated (c.f. section 3.2.5).

There are further concerns about the painDetect versions of the headache questionnaires MIDAS and EHI. While the questionnaires themselves are well validated, the computerized versions are not cross-validated with the paper-pencil version. It thus cannot be claimed with certainty, that the results from the computerized baseline assessment and from the postal follow-up assessment are absolutely equivalent. Those tools of the painDetect software, which are cross-validated, but not used for this study, tested without significant difference to the paper-pencil version, though (Junker et al., 2008). This result excludes at least a general distortional effect of the handheld device.

6.5.4 No overall Regression Model

The study design with two phases resulted in some constraints to the data analysis (cf. Figure 3 in section 3.1). As a consequence of the differing sample sizes for the NEO-FFI, BriefCOPE and PCS, it
was not possible to calculate an overall regression model. It thus remains unclear how much of the variance of headache in patients with TSR would be explained by all the investigated psychological factors combined. And although the parameter estimates in the individual regression models give some clues as to the importance of the psychological factors, a definite statement on the overall order of the factors cannot be made by this study. This has to be left open to future investigations.

6.5.5 No Control Group

While it was not the main objective of the present thesis, a comparison of the sample to an untreated control group would have been of interest. Especially the interpretation of treatment effects could have been strengthened by a comparison to untreated patients. The description of headache characteristics would in turn have benefitted from a comparison to a control group of patients with primary headache. This would have also allowed a comparison of the influencing factors between primary headache and headache in patients with TSR. However, a control group is hard to come by in a neurosurgical clinic. In the light of limited resources, it was decided to enlarge the TSR treatment sample to a size allowing for regression analyses, rather than to invest resources into a control group, since the former was of more importance to the study objectives.

6.6 Conclusion

The present thesis proposed a biopsychosocial explanatory model for headache in patients with TSR. It was the main aim of the study to find evidence for a psychological component in the causation of headache in this patient group. The results of the study clearly confirmed the influence of personality, stress coping and pain catastrophizing on headache in patients with TSR. Occurrence of headache, disability due to headache and change in disability due to headache after neurosurgery were all significantly affected by psychological variables. It was discussed in which way psychological factors could be addressed in the diagnosis and treatment of headache in patients with TSR as well as in daily clinical practice. Several open research questions for the further investigation of the causes of headache in patients with TSR were derived from the proposed biopsychosocial model. Additionally, headache characteristics and treatment response to neurosurgery were described in detail. The resulting clinical picture of headache in patients with TSR was strikingly heterogeneous. The resulting difficulties in the diagnosis of headache directly attributed to TSR were pointed out. It was suggested, that its prevalence has previously been overestimated. The results clearly support the need for sufficient indication for neurosurgery apart from headache to justify tumor removal in headache in patients with TSR.
7 Summary

Background. It was the aim of the present thesis to investigate the influence of a psychological component on the occurrence of headache, disability due to headache and treatment response of headache to neurosurgery in patients with tumors of the sellar region (TSR). With an observed prevalence of up to 70% headache is a common symptom in patients with TSR. It has previously been entirely attributed to pathophysiological mechanisms. Earlier studies investigated mechanical pressure due to tumor size, intrasellar pressure and endocrine hypersecretion as possible causes for pain, but the results stayed largely inconclusive. The present thesis is the first to introduce a biopsychosocial model to the explanation of headache in patients with TSR.

Methods. 112 patients with TSR prior to first-time neurosurgery received questionnaires on personality (NEO Five-Factor Inventory, NEO-FFI), headache characteristics (Essen Headache Inventory, EHI) and disability due to headache (Migraine Disability Assessment, MIDAS). A subsample of 71 patients was additionally questioned on stress coping (BriefCOPE) and pain catastrophizing (Pain Catastrophizing Scale, PCS). Headache characteristics in 68 patients were assessed for a second time on average 7.1 months after neurosurgery. Occurrence of headache within the last three months and disability due to headache as indicated by the MIDAS score were used as criteria variables in logistic regression models. Change in MIDAS score after neurosurgery was correlated to potential psychological influencing factors.

Results. Logistic regression analyses revealed that conscientiousness, neuroticism and pain catastrophizing were significant predictors of headache occurrence, whereas neuroticism, pain catastrophizing and humor predicted disability due to headache. There was no significant effect of neurosurgery on the occurrence of headache. Disability due to headache was not significantly reduced after neurosurgery, either. Individual change in disability due to headache after neurosurgery correlated positively to extraversion and negatively to neuroticism, behavioral disengagement and humor.

Discussion. The results clearly support the theory of a psychological influence on headache in patients with TSR. They suggest that physicians involved in the clinical treatment of TSR should refrain from purely mechanistic explanations of headache. They also lend further strength to the argument, that neurosurgery should not be performed due to headache alone and integrative treatment approaches for headache in patients with TSR should be considered. The derived biopsychosocial model raises a multitude of further research questions, which could help to elucidate the as yet unclear specifics of the causation of headache in patients with TSR.
References


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**Appendix A: List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
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<td>ADH</td>
<td>antidiuretic hormone</td>
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<td>CBT</td>
<td>cognitive-behavioral therapy</td>
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<td>CRH</td>
<td>corticotropin-releasing hormone</td>
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<td>CSF</td>
<td>cerebrospinal fluid examination</td>
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<tr>
<td>CT</td>
<td>X-ray computed tomography</td>
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<td>EEG</td>
<td>electroencephalography</td>
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<td>EHI</td>
<td>Essen Headache Inventory</td>
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<td>FSH</td>
<td>follicle-stimulating hormone</td>
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<td>GH</td>
<td>growth hormone</td>
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<td>GHRH</td>
<td>growth hormone-releasing hormone</td>
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<td>gonadotropin-releasing hormone</td>
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<td>HIT-6</td>
<td>Headache Impact Test</td>
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<td>ICHD-3</td>
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<td>LH</td>
<td>luteinizing hormone</td>
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<td>MIDAS</td>
<td>Migraine Disability Assessment</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NEO-FFI</td>
<td>NEO-Five Factor Inventory</td>
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<td>NHP</td>
<td>Nottingham Health Profile</td>
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<td>PCS</td>
<td>Pain Catastrophizing Scale</td>
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<td>Patient's Health Questionnaire</td>
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<td>recombinant human growth hormone</td>
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<td>somatostatin analogue</td>
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<td>TSR</td>
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<td>TTH</td>
<td>tension-type headache</td>
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<td>VAS</td>
<td>visual analogue scale</td>
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<td>WHO</td>
<td>World Health Organization</td>
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### Appendix B: Additional Statistics

#### Table B1

**Intercorrelations between predictor variables**

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<th></th>
<th>NEO-FFI</th>
<th>PCS Total</th>
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**Note.** NEO-FFI = NEO-Five Factor Inventory; N = neuroticism; E = extraversion; O = openness to experience; C = conscientiousness; A = agreeableness; PCS = Pain Catastrophizing Scale; D = denial; SU = substance use; BD = behavioral disengagement; PR = positive reframing; H = humor; SB = self-blame; *p<0.05. **p<0.01. ***p<0.001
Table B2

Two-sample t-test for the Comparison of Pain Catastrophizing between Patients with different Reasons for the Conduction of MRI (post-hoc analysis)

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Note. MRI = magnetic resonance imaging; PCS = Pain Catastrophizing Scale.
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Curriculum Vitae

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.