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Personality and Autonomy in Light of Neuroscience. Ethical and Neurophilosophical Issues of Interventions in the Brain

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Content

0. List of Acronyms

AC	Alternating current
ALIC	Anterior limb of internal capsule
BIID	Body Integrity Identity Disorder
CT	Computed tomography
DBS	Deep brain stimulation
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DTI	Diffusion tensor imaging
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
HRQOL	Health-related quality of life
ICD 10	International Statistical Classification of Diseases and Related Health Problems, 10th edition
ICF	International Classification of Functioning, Disability and Health
ITP	Inferior thalamic peduncle
MDD	Major depressive disorder
MFB	Medial forebrain bundle
MFH	Magnetic Fluid Hyperthermia
MFH 300F®	Magnetic Fluid Hyperthermia whole body magnetic field applicator
MRI	Magnetic resonance imaging
n	Number of patients
NAcc	Nucleus accumbens
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
OS-2	Overall survival following diagnosis of first tumor recurrence
PTSD	Post-traumatic stress disorder
PD	Parkinson’s disease
PET	Positron emission tomography
PPN	Nucleus pedunculo pontinus
PVS	Persistent vegetative state
QoL	Quality of life
rTMS	Repetitive transcranial magnetic stimulation
SCC	Subcallosal cingulate
SE	Side effects
slMFB	Supero-lateral medial forebrain bundle
SPECT	Single-photon emission computed tomography
STN	Nucleus subthalamicus
VC	Ventral capsule
Vim	Ventral intermediate part of the thalamus
vmPFC	Ventromedial prefrontal cortex
VS	Ventral striatum
VTA	Ventral tegmental area

1. Introduction

Neurosurgical interventions in the brain have the potential to change fundamental mental properties, in particular cognitive abilities, affective states, and the capability for autonomy, and even the personality as understood in psychiatry.[1] The focus of this work is on changes in personality and on alterations of the capability for autonomy caused by neurosurgical[2] interventions; the predominant goal of the following chapters is the ethical analysis of suchlike interventions. The ethical analysis is grounded in a neurophilosophical approach which assumes that all aspects of personhood depend on the state of the brain (which again is influenced by the state of the body and by the natural and social surrounding), and thus can be changed (at least in principle) by neurological or psychiatric disorders as well as by physical or chemical modifications of the brain, regardless whether they occur naturally, traumatically, or through intervention. Under this perspective, interventions in the brain are generally regarded as potential interventions in the person and thus as an enormous ethical challenge. Dualistic concepts which suggest that the brain is physical and the mind is spiritual fail to recognize the particular ethical challenge of interventions in the brain.

Modern neurosurgery has established quite new possibilities for the therapy of diseases and traumata of the brain. On the one hand, it offers important chances: lifesaving, healing or palliation of severe neurological disorders, prevention or cure of disabilities, therapy of pain and possibly of certain mental disorders. On the other hand, neurosurgical interventions still bear the risk of mortality and of severe morbidity, e.g., sensory or motor dysfunctions, paralyses, long-lasting coma, locked-in syndrome, memory loss, cognitive decline, and affective and behavioral sequelae.

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[1] Psychological research on personality is very heterogeneous (e.g., Asendorpf 2007; Amelang & Bartussek 2001; Myers 2008). Important approaches are Freud's psychoanalytical theory of personality, Maslow's and Rogers' humanistic personality psychology (Maslow 1970; Rogers 1980), Bandura's social-cognitive approach (Bandura 1986 and 2001), and Eysenck's personality theory (Eysenck 1953 and 1967). In modern psychiatry, the differential psychology developed by Allport et al. (1937) plays the greatest role. According to this theory, each individual personality is characterized by basic properties (*traits*) which manifest themselves in temporarily stable patterns of behavior. Costa and McCrae (1992) have developed the empirically founded Five Factor Model of personality ("Big Five"). Thereafter, the personality of an individual can be described by the following five dimensions of personality (traits): openness, conscientiousness, extraversion, agreeableness, and neuroticism. For determining personality traits, particularly the Minnesota Multiphasic Personality Inventory (MMPI) (Hathaway & McKinley 1989) and the NEO Five-Factor Inventory (NEO-FFI) (Costa & McCrae 1992) are used. Originally, the traits had been understood as stable, mostly genetically determined properties, but recent research has shown that they can change till old age (Roberts & Mroszek 2008). In how far traits can be changed by interventions in the brain, has hardly been investigated yet. — Since the Big Five model is broadly accepted in contemporary psychology and psychiatry, I will use the term "personality" in the latter sense, if not mentioned otherwise.

[2] In the following, the term "neurosurgery" is used in a broad sense, i.e., it includes interventions in the brain through microsurgery, radiosurgery (Gamma Knife, CyberKnife, Heavy Ion or Proton Radiotherapy), thermal ablation, stereotactic-focused ultrasound, and deep brain stimulation.

It is important to recognize that neurosurgical interventions imply both the *risk* and the *chance* of changing cognitive or affective functions, the behavior, or the personality. Neurosurgery has become a mighty tool; but it is a two-sided weapon, which raises hope and induces angst. Therefore it requires a particular ethical reflection.

Ethical issues of therapeutic interventions in the brain can be summed up in the following categories:

1. Their *goal* (e.g., to save life, to heal disabling diseases, to enhance the mood, or to modify certain personality traits)
2. Their *means* (e.g., surgery, pharmaceutics, herbal drugs, or psychotherapy)
3. Their *effectiveness* (i.e., whether and to which extent the goal is achieved)
4. Their *efficiency* (i.e., the benefit-cost-relationship)
5. Their *risks and adverse effects* (e.g., mortality, de novo neurological or psychiatric disorders)
6. The *potential consequences for society and environment* (e.g., financial burdens for the society, allocation issues, social pressure, environmental risks).

An ethical evaluation of neurosurgical interventions requires differentiating unintended intervention-related mental changes from intended ones (Müller S 2007):

1. *Unintended* mental changes may occur as side effects or may be caused by complications of microsurgery, radiosurgery, or radiotherapy, e.g., as consequences of oedemas, liquor accumulation, increased brain pressure, surgery-related lesions, radiation necrosis, or inflammations.

2. *Intended* are mental changes if brain lesions or diseases (e.g., brain traumata, brain tumors, strokes, degenerative brain diseases, encephalitis, or meningitis) are supposed to be the cause of a mental disorder which might be cured by an intervention. Under the paradigm of biological psychiatry (Walter 2013) also psychiatric disorders are understood as brain diseases, although their aetiology is not well understood. This paradigm supposes therapies of the brain in order to treat mental disorders, psychotropic drugs as well as neurosurgical interventions. Particularly, psychiatric neurosurgery directly intends to cause personality changes by undoing pathological changes (Nuttin et al. 2014).

The following chapters investigate both interventions which can cause unintended mental changes and interventions which directly aim at changing certain aspects of the mental state, the personality or the behavior.

1.1 From psychosurgery to psychiatric neurosurgery

Psychosurgery has been defined explicitly by the goal "to control, change, or affect any behavioral or emotional disturbances" by stimulation or surgery of the brain (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research 1977). Modern psychiatric neurosurgery comprises stereotactic ablative procedures, thermal ablation, radiosurgery (e.g., Gamma Knife), stereotactic-focused ultrasound, and electrical stimulation of the brain by implanted electrodes.

The old term "psychosurgery" seems to be based on a differentiation between psychiatric and neurological diseases, or between the mind and the brain. With shifting the boundaries between "psychiatric" and "neurological" disorders, also the classification of a given brain intervention as "psychosurgery" will shift. By way of example, Parkinsonism has been classified in the past as a neurological disorder; today it is seen as a neuropsychiatric disorder (Temel et al. 2005; Voon et al. 2006). In the past, neurosurgery for psychiatric conditions was generally viewed as procedures performed on structurally normal tissue, whereas neurosurgery for neurological disorders was seen as procedures performed on structurally abnormal tissues. The usefulness of this differentiation has become obsolete since, for example, neurosurgery for Parkinson disease is undertaken with the intent of destroying functionally and structurally normal brain tissue that has become disinhibited due to pathological conditions elsewhere in the brain (Feldman et al. 2001).

Psychosurgery, i.e. ablative neurosurgery to treat mental disorders, had an enthusiastic rise and a dramatic fall between the 1930ies and the 1970ies.[3] Both, its rise and fall, are connected with its enormous potential of changing the personality and behavior of persons. A coarse-grained understanding of neuroanatomical and physiological underpinnings of psychiatric disorders and the discovery that destroying certain critical brain areas could ameliorate certain psychiatric symptoms, had encouraged physicians to destroy brain tissue of psychiatric patients in a brute and shirt-sleeve manner. The so-called topectomy (invented by Gottlieb Burckhard in 1888 in Switzerland) consists in excising multiple foci of the frontal, parietal and temporal cortices. The "frontal lobotomy" (developed by Egas Moniz in 1935 in Portugal) required the excision of both afferent and efferent fibres of the frontal lobe. A modified procedure was the "frontal leucotomy" (developed in 1935 by Egas Moniz and Almeida Lima in Portugal), which was performed by injecting alcohol into the white matter of the frontal lobe. After the introduction of the lobotomy to the United States by Walter Freeman and James Watts in 1936, Freeman popularized the "transorbital lobotomy" based on a technique developed by Amarro Fiamberti in Italy.

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[3] For the history of psychosurgery see Feldman & Goodrich 2001; Fins 2003a; Heller et al. 2006; Kopell & Rezai 2003; Mashour et al. 2005; Robison et al. 2012; Sachdev & Chen 2008; Wind & Anderson 2008.

Many targets, approaches, and techniques had been tried, with diverse and sometimes contradictory outcomes. The spectrum of psychiatric disorders treated with these procedures was rapidly broadened and comprised anxiety and mood disorders, schizophrenia and childhood behavior disorders, but also homosexuality and criminal behavior. Serious postoperative complications were reported such as hemorrhage, seizures, intellectual impairment, paralysis, urine incontinence, and death. Furthermore, negative personality changes occurred, e.g., disinhibition, apathy, depression, indifference, lack of initiative, judgment and self-criticism, decrease of initiative and energy level, and personality change of the "frontal lobe type". Because of its frequent negative effects on the personality and its severe sequelae, frontal lobotomy and other forms of ablative psychosurgery became discredited and were nearly completely abandoned (reviews: Andrade et al. 2010; Feldman et al. 2001; Greenberg et al. 2010; Sachdev & Hay 1995; Sakas et al. 2007).

Today, the terms "psychiatric neurosurgery" and "neurosurgery for mental disorders" have largely replaced the discredited term "psychosurgery" to describe modern neurosurgical therapies of psychiatric disorders which are highly refined, much safer and more effective. The improvements are based on the refinement of surgical techniques, the usage of neuro-imaging technologies and stereotactic methods for the accurate placement of lesions, and the introduction of radiosurgery. These developments have substantially reduced the risks of adverse effects of neurosurgical procedures and thus allowed for transferring neurosurgery for treating psychiatric disorders into the modern era.

Nowadays, the dominating methods are anterior cingulotomy, subcaudatetractotomy, anterior capsulotomy (performed by either mechanical lesioning, thermal ablation or Gamma Knife radiation), and limbic leucotomy (D'Astous et al. 2013; Feldman et al. 2001; Greenberg et al. 2003 and 2010; Sachdev & Chen 2008; Sakas et al. 2007). Ablative neurosurgery for treating psychiatric disorders is offered only in very few centres (Nuttin et al. 2014) for a small number of patients, particularly as a treatment of last resort for affective disorders, anxiety, and obsessive-compulsive disorders (OCD) (Bridges et al. 1994; D'Astous et al. 2013; Feldman et al. 2001; Greenberg et al. 2003 and 2010; Kim et al. 2003; Jung et al. 2006; Rosenfeld & Lloyd 1999; Sachdev & Hay 1995). A handful of papers report its use for treating eating, psychosexual, drug abuse and impulse control disorders (reviews: Feldman et al. 2001; Patel et al. 2013; for depression and OCD: Eljamel 2008; for addiction: Stelten et al. 2008). Recently, a Belgian case study has reported a patient with comorbid anorexia nervosa and OCD who was successfully treated with anterior capsulotomy (Barbier et al. 2011).[4] And

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[4] The patient could not comply for practical reasons with the hospital's strict follow-up protocol for DBS.

a Chinese study has reported the successful treatment of drug addicts by ablation of the ventromedial shell of the nucleus accumbens (Yang et al. 2014).[5]

According to a meta-analysis of Leiphart and Valone (2010), anxiety disorders (general anxiety disorder and OCD) had the greatest reported improvements from anterior capsulotomy, whereas mood disorders (bipolar disorder, depression) and schizoaffective disorder profited most from anterior cingulotomy. Addiction and schizophrenia showed the least improvements from stereotactic surgery.[6]

The safety and efficacy of current practised stereotactic ablative procedures are supported by level II evidence in treatment-refractory MDD and OCD; whereas for lesioning methods such as Gamma Knife and stereotactic-focused ultrasound this degree of evidence is not yet available (Nuttin et al. 2014). A recent review on radiosurgery for the treatment of psychiatric disorders (Lévèque et al. 2013, n = 49) found response rates of 55% to 70% in patients with different diagnoses treated with Gamma Knife anterior capsulotomy. Unfortunately, there is a lack of standardization (particularly with regard to the radiation dose and the exact target) and in most cases a poor neuropsychological testing.

Since the currently used lesioning methods cause smaller cerebral lesions than the earlier procedures, they have lesser side effects, primarily less deficits in emotional reactivity and motivation (Polosan et al. 2003). Nevertheless, adverse neurological or mental sequelae are reported. For example, permanent post-capsulotomy complications are hemiparesis, seizures, urinary disturbances, memory deficits, loss of initiative, fatigue, apathy, aggressiveness, dysexecutive function behavior, and sexual disinhibition (Cosgrove & Rauch 1995; D'Astous et al. 2013; Dougherty et al. 2002; Feldman et al. 2001; Rück et al. 2008).

Since 1999, DBS is increasingly investigated as a therapy option for severe, intractable psychiatric disorders (reviews: Goodman & Alterman 2012; Holtzheimer & Mayberg 2011; Krack et al. 2010; Kuhn et al. 2010; Schläpfer & Kayser 2010), primarily OCD (reviews: De Koning et al. 2011; Haynes & Mallet 2010; Mian et al. 2010) and major depressive disorder (reviews: Anderson et al. 2012; Andrade et al. 2010). The application of DBS to psychiatric disorders is based on clinical experiences with DBS which is used since the 1980ies for treating patients suffering from Parkinson's disease, dystonia or essential tremor. Worldwide, more than 100,000 patients have been treated with DBS until 2014 (Medtronic).[7]

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[5] 80 % of 65 patients did no longer experience craving for the drugs after surgery.

[6] The meta-analysis of Leiphart & Valone (2010) has reviewed proceedings from the World Congresses of Psychiatric Surgery from 1970 to 1978 and from a PubMed search. Strict inclusion criteria were used. Reports about disorders with fewer than 10 patients were not analyzed due to their low statistical power. Finally, data from 28 studies was used that comprised 1,145 patients who were treated with stereotactic lesions targeting various anatomical foci. The data was standardized using a 5-point scale (3 [free of symptoms] to -1 [worse]).

[7] www.medtronicdbs.com/parkinsons/about/benefits-and-safety/index.htm (accessed: 07.02.2014).

A PubMed search returned 18 papers about DBS for obsessive-compulsive disorder (OCD) and 12 papers about DBS for major depressive disorder (MDD) (published before Nov 20, 2013).[8] The papers on OCD report altogether minimally 71 and maximally 83 patients; the papers on MDD minimally 63 and maximally 113 patients.[9]

The results of DBS for psychiatric disorders are heterogeneous, but look promising for some indications. The spectrum of novel DBS indications is rapidly expanding; it comprises Tourette's syndrome (review: Müller-Vahl 2013), aggressive and disruptive behavior (Franzini et al. 2012), drug addiction (Kuhn et al. 2007 and 2009a; Langevin 2012;[10] Mantione et al. 2010; Müller UJ et al. 2009; Valencia-Alfonso et al. 2012; Zhou et al. 2011; reviews: Bauer et al. 2008; Halpern et al. 2011; Luigjes et al. 2012), severe obesity (Hamani et al. 2008; Whiting et al. 2013; review: Halpern et al. 2011), anorexia nervosa (Lipsman et al. 2013; Wu et al. 2013; Wang et al. 2013), and Alzheimer's disease (reviews: Laxton & Lozano 2013; Hesham et al. 2013).

In spite of the successful use of DBS, its mechanisms of action continue to be debated in the scientific community (McIntyre et al. 2004).[11] According to Haynes & Mallet (2010), the use of DBS is more empirical than based on a strong scientific explanation.[12]

Although the targeting of the DBS electrodes for treating psychiatric diseases is to a great extend based on the ablative psychosurgery literature, new targets have been detected by novel methods as neuroimaging studies and tractographs (Sachdev & Chen 2008). The spectrum of targets of psychiatric DBS is broad, too, indicating the still exploratory state of research. By way of example, for treating OCD, five different targets have been addressed: nucleus accumbens (NAcc), anterior limb of internal capsule (ALIC), ventral capsule/ventral striatum (VC/VS), nucleus subthalamicus (STN), and inferior thalamic peduncle (ITP) (De Koning et al. 2011; Goodman & Alterman 2012). For major depressive disorder, five different targets have been tested: subgenual cingulate cortex, VC/VS, NAcc, ITP, and lateral habenula

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[8] The search included only studies with patients with the main diagnosis OCD or unipolar major depression respectively. It was restricted to papers in English and German.

[9] Since several papers from the same groups seem to report the same patients several times (although this is generally not documented), the numbers of patients cannot be summarized exactly, but only the maximal and minimal numbers.

[10] In contrast to the other DBS studies for treating addiction which have used the nucleus accumbens as stimulation target, Langevin (2012) has stimulated the amygdala. This proposition is based on the hypothesis that the amygdala plays a critical role in certain forms of relapse related to exposure of reminders of drug intake or drug withdrawal. Therefore DBS of the amygdala could reduce the incidence of relapse.

[11] Four general hypotheses are discussed to explain the mechanisms of DBS: depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathologic network activity (McIntyre et al. 2004).

[12] DBS has most probably not a simple inhibitory effect, as was first proposed, but a complex effect, combining inhibition of spontaneous local activity with imposition of high-frequency discharge because of decoupled soma and axons, and antidromic or orthodromic activations of different subsets of neurons according to their intrinsic properties (e.g., myelinization), modulated by their various collaterals. DBS could serve to restore the STN's control over decision-making and behavioral output, or to rebalance the different pathways, generally through an increase in dopamine concentrations in the striatum (Haynes & Mallet 2010).

(review: Anderson et al. 2012). Recently, a sixth target has been addressed, namely the supero-lateral branch of the medial forebrain bundle (slMFB) (Schläpfer et al. 2013).[13] Although the findings are preliminary (only seven patients), they suggest that the slMFB might be the "master target" for several reasons: First, the onset of the antidepressant effect was rapid (days instead of months), the proportion of responders (86%) was significantly higher than in previous studies, and a lower stimulation current intensity was required than in former studies (about one-third).

Remarkably, in several cases, not the disorder addressed (e.g., anxiety or OCD) was cured by DBS, but a comorbid disorder resolved (e.g., addiction to alcohol or nicotine) (Krack et al. 2010; Kuhn et al. 2007 and 2009a). In one case, DBS of the fornix failed to treat obesity, but instead enhanced the patient's (good) memory (Hamani et al. 2008); this surprising result inspired the first clinical study on DBS for the treatment of Alzheimer's disease (Laxton et al. 2010). In a number of cases, both the disorder addressed and a comorbid disorder resolved, e.g., OCD and anorexia (McLaughlin et al. 2013), or OCD, nicotine addiction and obesity (Mantione et al. 2010).

Since not all psychiatric DBS case studies have been published, but mainly the successful ones as well as those with a surprising but positive outcome, a publication bias exists which might let people overestimate the success rate of psychiatric DBS (Schläpfer & Fins 2010).

At present, the field of psychiatric DBS is in a fast developing, experimental stage. Whether DBS will become a successful treatment option for severe, otherwise treatment-resistant psychiatric disorders will depend primarily on the understanding of the anatomy and the pathophysiology of the underlying conditions. This knowledge would help translate psychiatric illnesses in "neurosurgical terms," and thus allow for identifying and intervening in the areas of the brain most responsible for the dysfunction (Langevin 2012).

Only a few commentators consider psychiatric DBS as a continuation of the discredited historical psychosurgery (e.g., Adler 2004; Meier 2009). Nevertheless, Carter & Hall (2011) demand a moratorium for clinical research in treating addiction with DBS, because the history of neurosurgery warned against acceptance of early 'positive results' in uncontrolled, possibly selectively reported cases. Most authors reflect the historical background of DBS, but highlight the important differences between previous psychosurgery and DBS with regard to invasiveness, reversibility, adjustability, and orientation to the principles of beneficence and patient's autonomy (Arends et al. 2009; Bauer et al. 2008; Fins 2003a; Fins et al. 2006; Greenberg et al. 2003 and 2010; Heller et al. 2006; Huys & Müller 2013; Illes 2012; Kuhn et

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[13] Through the MFB, the NAcc, the ventral tegmental area, the ventromedial and lateral nuclei of the hypothalamus and the amygdala are interconnected. The supero-lateral branch of the medial forebrain bundle (slMFB) converges onto the prefrontal cortex and has close functional connection to previously suggested DBS sites for depression (Schläpfer et al. 2013).

al. 2009b; Müller S 2007; Sachdev & Chen 2008; Sakas et al. 2007; Synofzik & Schläpfer 2008; Tye et al. 2009; Wiesing 2010).

In spite of the advent of DBS, lesioning procedures (performed by either microsurgery or Gamma Knife) are seen by some experts as an important alternative for appropriately selected patients with otherwise intractable diseases (for Parkinsonism: Bronstein et al. 2011; for psychiatric disorders, particularly OCD or anorexia nervosa: Barbier et al. 2011; D'Astous et al. 2013; Greenberg et al. 2003 and 2010; Lévèque et al. 2013; Mathews et al. 2011). Recently, an international expert panel has stated in a consensus paper[14] that "until scientifically proven otherwise, DBS is not superior to ablative surgery for psychiatric disorders" (Nuttin et al. 2014). The main reasons against abandoning ablative procedures are first the relative low cost, second certain exclusion criteria or practical limitations of DBS. For example, DBS is not indicated for patients who would not tolerate implanted devices (e.g., patients with compulsive skin-picking) and for patients with especial infection risks.[15] Practically, DBS is not useful for patients who live in remote areas or would not comply with the long-term follow-up after DBS. A further advantage of lesioning methods as opposed to DBS is that they do not exclude future treatments with electroconvulsive therapy (Eljamel 2008). Particularly, Gamma Knife or CyberKnife radiosurgery offers a unique advantage: Since it does not require a craniotomy, the risks of anesthesia, hemorrhage and infection do not exist. Therefore radiosurgery could be an alternative for patients who could tolerate neither the stress of a wake-operation nor an operation under general anesthesia. Another advantage is that radiosurgery is normally performed as an ambulatory treatment. On the other hand, DBS has the great advantages of reversibility (at least in principle) and modifiability.

Nevertheless, major ethical issues remain: Can it be ethically justified to manipulate the personality and the behavior of a person through direct interventions in the brain? Can neurosurgery be justified for treating mental disorders (particularly addiction)? Could neurosurgery be justified for enhancement? How can informed consent be guaranteed, particularly for psychiatric patients, if information about possible changes in personality and behavior is scarce, and if the ability to consent may be affected by the disorder? How can possible

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[14] The paper (Nuttin et al. 2014) articulates a consensus summary of the following organizations: Committee for Neurosurgery for Psychiatric Disorders, as part of the World Society for Stereotactic and Functional Neurosurgery (WSSFN) and the European Society for Stereotactic and Functional Neurosurgery (ESSFN); Working Group 'Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application'; Psychiatric Neurosurgery Committee of the American Society for Stereotactic and Functional Neurosurgery (ASSFN); Latin American Society for Stereotactic and Functional Neurosurgery (SLANFE); Asian-Australasian Society for Stereotactic and Functional Neurosurgery (AASSFN); World Psychiatric Association (WPA).

[15] By way of example, patients with Tourette's syndrome have a much higher infectious rate (18%) than patients with other movement disorders (3.7%). This might be due to abnormalities of the immune system or behavioral features such as a compulsive drive to touch the scar tissue (Müller-Vahl 2013). This could speak in favor of Gamma Knife instead of DBS for Tourette patients. ─ Kondziolka et al. (2011) have described an OCD patient with compulsive skin-picking who could not tolerate the implanted DBS system and was successfully treated with radiosurgery.

changes in personality or behavior be evaluated? Who should decide about the fine-tuning of the patients' personalities? How should physicians deal with therapy-induced mental changes which are regarded as problematic by either society or the patients or their families?

The more precise and the less invasive interventions in the brain become and the better the understanding of the neuroanatomical and physiological background of neurological and psychiatric disorders becomes, the more will neurosurgical interventions become standard therapeutic options for certain neurological and psychiatric disorders. Neurosurgery will not be used only for treating life-threatening brain disorders or lesions, but more and more for improving certain abilities or the quality of life of neurological and psychiatric patients. Consequently, the use of deep brain stimulation and of radiosurgery for the purpose of neuro-enhancement has been discussed yet (e.g., Hildt 2006; Lipsman et al. 2009; Lipsman & Bernstein 2011; Pacholczyk 2011; Synofzik & Schläpfer 2008; Synofzik et al. 2012) as well as for the purpose of treating "moral dysfunction" (De Ridder et al. 2009). Although this looks utopian, the broadening of the spectrum of neurosurgical treatments requires an ethical analysis that anticipates suchlike future applications, too, and develops solutions for problems at best before they occur and in order to prevent their occurrence.

1.2 Why are personality changes caused by interventions in the brain an ethical issue at all?

Within the framework of dualistic mind-brain-theories, interventions in the brain do not raise fundamentally different ethical issues than, by way of example, interventions in the heart. But dualistic mind-brain-theories are disproved by many empirical findings; nowadays they are vastly seen as obsolete in science. Within a genetic framework of personality, too, interventions in the brain cannot be understood as crucial for severe personality changes. This is also valid for common traits personality theories, e.g., the Five Factor model (Costa & McCrae 1992). Trait theories describe personality traits as deeply rooted, substantially fixed, highly stable, primarily genetic in origin, and largely immune to culture and individual experience; thus they conceptualize traits as if they were essences (Haslam et al. 2004). Trait theories consider only the normal brain development, not the consequences of severe diseases or lesions of the brain.

Only in a framework of a neuroscientific model of persons (e.g., Damasio 1999; Metzinger, ed., 1996; Newen & Vogeley 2000; Walter 2001 and 2004; Pauen & Roth 2008) it is understandable that interventions in the brain may indeed be interventions in the personality and the core capacities of persons, particularly cognition, emotionality, memory, and the capability for autonomy. Neurophilosophical models describe persons as dynamic biological systems with certain abilities of self-representation and self-regulation. According to these models, the person or the self is not a monolithic entity, but composed of different modules which act on different levels of functional and representative complexity. Instead of the obsolete dualism of ‘personality-relevant’ and ‘personality-neutral’ brain areas, these models comprise continuous systems from basic sensory-motor functions to complex affective and cognitive functions interacting both top-down and bottom-up. These neurophilosophical models of the self make also understandable why interventions in apparently mere motor areas can cause mental changes. Principally, alterations of mental functions have to be anticipated for most physical or chemical interventions in the brain (Müller S 2007). Therefore, only in such a framework, interventions in the brain raise specific and severe ethical questions (Ford & Henderson 2006; Northoff 2001; Vogeley & Newen 2011).

Since neurosurgically caused personality changes are not a matter of fate (as opposed to those caused by brain traumata or brain diseases), but consequences of conscious decisions and actions of persons, and since their possible occurrence can be anticipated, decisions about interventions in the brain generally have to be evaluated *ethically*.

But not only interventions in the brain, but also their waiving may bear severe risks, not only of mortality and morbidity, but also of personality changes or the loss of the capability for autonomy, which might be preventable by an intervention. Therefore it is important to note that not only interventions in the brain, but also their waiving can be ethically problematic (Müller S 2007). This aspect is sometimes overlooked in bioethical debates since they often focus more on the risks of the usage (and abuse) of new technologies than on the consequences of their non-usage (Müller S 2009d). Neuroethicist Joseph Fins has rightly criticized that in the current ethical taxonomy risk-aversion dominates over appreciation of potential benefits of new therapeutic approaches for patients with impaired decision-making (Fins 2003b). Thus, overstressing the principle of non-maleficence may have the unintended effect that patients with certain brain diseases are deprived of interventions which could restore their cognitive or affective functions. Therefore, it is important to balance both risks and chances in an ethical evaluation, especially with regard to possible changes in personality or the capability for autonomy.

Neurosurgically caused (and generally iatrogenic) personality changes pose difficult neuroethical questions:

- What is at stake through brain interventions: the identity of the person, the personal identity, or the personality?
- Should the personal identity or the personality, respectively, be protected generally?

- How should antidromic goals as the conservation of the personal identity or the personality, respectively, on the one hand and the maintenance of life on the other hand be balanced against each other?
- Are neurosurgical interventions which imply a *risk* of personality changes ethically arguable, and if so, under which conditions?
- Are neurosurgical interventions with the primary *aim* of personality changes arguable, and if so, under which conditions?
- According to which criteria should personality changes be evaluated?
- How is it possible to evaluate the capability for autonomous decision-making of patients with brain diseases or lesions? How can it be protected best, if both the disease and the therapeutic intervention threaten this capability?
- How should be dealt with personalities with a neurological disposition of behavior which regularly harms third persons?
- How can neurosurgical interventions affect the moral and/or legal responsibility?

These neuroethical questions lead directly into the centre of the philosophy of mind and of neurophilosophy: What is meant by the terms *person*, *personal identity*, and *personality*? In how far does the personal identity or the personality, respectively, depend on the identity of the brain? What has to be understood by these terms in light of neuroscience, especially with regard to neurologically caused or iatrogenic personality changes? Furthermore, these issues challenge medical ethics since they demand for an in-depth-analysis of the concepts *autonomy*, *capability for autonomous decision making*, *responsibility* and *authenticity.*

1.3 Are interventions which might cause personality changes generally unethical?

Given the high ethical valence of the concept of personality, the first intuition could be that interventions which might change the personality of another person are generally unethical.[16] But the fact that certain interventions in the brain may cause personality changes is no sufficient reason to condemn or to prohibit them for several reasons:

First, personality changes cannot be condemned per se because they also occur naturally, either because of drastic experiences, normal processes of maturation and aging, or brain diseases. For example, an overambitious, workaholic person may become lazy and hedonistic after an accident which nearly killed him; a friendly elder person can become hostile, suspicious and psychopathic through frontotemporal dementia. Second, personality changes cannot be evaluated negatively in general, since the latter personality may be better than the

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[16] Elisabeth Hildt (1999) holds the view that “identity conservation” (“Identitätserhalt”) should be a central ethical goal.

former one. *Therefore the mere possibility of personality changes is no argument against interventions which might cause such changes* (Müller S 2007; Müller & Christen 2011; see also: Baertschi et al. 2010; Brand 2009; Glannon 2010; Jotterand & Giordano 2011; Kraemer 2013; Nuttin et al. 2014; Synofzik & Schläpfer 2008).

According to another common position only personality changes caused by *intentional technical interventions* in the brain are ethically unacceptable. This position implies that naturally occurring personality changes (e.g., resulting from neurological disorders, brain traumata, brain cancer, or strokes) have to be accepted, even if they cause severe suffering and even if the person before the brain lesion would have disliked or even condemned the latter personality. This bioconservative position regards naturalness as an a priori value; insofar it is dogmatic. Although this may be a legitimate personal opinion of an individual patient, it cannot be the fundamental philosophy of medicine, since the very goal of medicine is to heal naturally occurring diseases.

Many brain diseases and lesions deeply affect the personality. For example, Parkinson's disease makes many patients depressive, apathetic, rigorous, anhedonic, or compulsive (Kulisevsky et al. 2008). Several brain disorders, particularly frontotemporal or vascular dementia, can cause sexual disorders, e.g., pedophilic behavior; the same is valid for the common medical treatment of Parkinson's disease (Mendez & Shapira 2011). Tumors in the temporal lobes can be associated with behavioral problems, including aggression and rage attacks (Nakaji et al. 2003). Also strokes can affect personality and behavior. For example, a 70-year-old man developed hemiballism, persistent hypersexuality, memory and executive dysfunction and poor judgment after a small stroke involving the STN (Absher et al. 2000). The behavior of patients with lesions in the orbitofrontal and ventromedial PFC has been described as aggressive, lacking responsibility and concern for social and moral rules (Eslinger & Damasio 1985; Damasio 1994). Patients with bilateral damage to the ventromedial prefrontal cortex and substance-addicted persons show similar behavior patterns related to dysfunction of the reflective system; both groups tend to seek immediate reward, even in spite of the risk of extremely negative future consequences (Burns & Bechara 2007). Also the moral judgment can be altered by lesions in the ventromedial prefrontal cortex (e.g., caused by a ruptured aneurysm of the anterior communicating artery): These patients tend more than controls to judge personal moral violations as acceptable behaviors (Ciaramelli et al. 2007); in particular, they produce an abnormally 'utilitarian' pattern of judgments on moral dilemmas, maybe because of diminished social emotion (Koenigs et al. 2007).

The waiving of effective cures of disease-caused personality changes conserves pathological personality traits even if the patient considers them as alien and suffers considerably from them. *Therefore, the waiving of an effective brain therapy can be ethically highly questionable just with regard to possible changes in personality.*

Finally, one could argue that only interventions which aim at *restoring* the original personality are ethically acceptable, whereas interventions aiming at a post-therapeutic personality, which differs considerably from both the original and the disease-altered personality, are unacceptable. Although this position is intuitive and looks sensible at the first glance, it faces at least three severe problems: first the difficult distinction between therapy and enhancement, second the difficulty to detect the "original" personality. The latter issue is especially relevant for patients suffering from chronic neuropsychiatric disorders, which rather cause subtle, lingering alterations than sudden, radical changes and do not have a clear starting point, as well as for persons who have a personality disorder since childhood (Müller & Christen 2011). Third, it is not arguable why just the patients' personality at the moment of the decision about an intervention in the brain should be morally distinguished. Taking into account that at the moment of the decision about a therapy, the patient's personality has yet been altered by the brain disease and that these changes are mostly unwanted, there is no reason to conserve the personality at that special moment.

Therefore, the aim to restore the personality to its pre-morbid state should be regarded only prima facie as a guiding principle. Obviously, it should be applied neither on cases of original personalities, which are not "good" (howsoever "good" is defined with regard to personalities), nor on interventions which could "improve" the personality.

One example may illustrate this argument: A patient who was dysphoric (but not clinically depressed) during his whole life became severely depressed by Parkinson's disease. After the implementation of a DBS system, two different stimulation settings are available which both cure the motor symptoms and the severe depression. But whereas the first setting would restore his dysphoric state, the second one would enhance his mood to a level which is normal for most people but not for him. According to the position which accepts only therapeutic interventions which restore but not enhance the original personality, the decision for the second option would be unethical (Müller & Christen 2011). Thus, this position demands the conservation of personality traits that are harmful for the patient insofar as they cause suffering or dysfunctional behavior.

Therefore, the ethically decisive question is not whether interventions in the brain can alter the personality or not, but whether they will do so in a good or bad way and whether the resulting effects on the personality are good or bad.

1.4 Current status of research on personality changes caused by interventions in the brain

Until now, cognitive, affective, and behavioral changes and personality changes caused by microsurgical or radiosurgical interventions in the brain have not been investigated comprehensively. In neurosurgery, the awareness of this kind of sequelae is still under-developed. Clinical research on mental changes following interventions in the brain is meagre in every respect (small numbers of cases, mostly retrospective studies, mostly without control groups, too short follow-up times), and does not fulfill the criteria of evidence-based medicine at all. This is not a mere scientific issue, but also an ethical problem: The severe knowledge deficits with regard to side effects of interventions in the brain, particularly with regard to the personality, force patients to make decisions with a high impact for their future life and possibly their future personality under high uncertainty.

In fact, research on DBS has the pioneer task in this field. The reason for that might be the fast investigational usage of DBS for a multitude of psychiatric indications. In light of historical psychosurgery, this development is politically explosive, and therefore several authors have uttered concerns that a misuse or an unqualified usage of DBS could lead to legislative restrictions (Fins et al. 2006; Fins 2009; Lieberman et al. 2008; Rabins et al. 2009; Sachdev 2007).

The range of personality changes caused by interventions in the brain is broad; subtle alterations as well as dramatic changes can occur. In severe cases, patients become alienated from themselves or are no longer recognized by their social surrounding as the same person as before the intervention (Schüpbach et al. 2006; Shamay-Tsoory et al. 2004; Tammer 2009). Some patients develop specific forms of emotional detachment. For example, a man lost selectively the emotional attachment to family members after right anterior temporal lobectomy (Devinsky et al. 2005). Another patient exhibited after temporal lobe surgery for epilepsy the Capgras syndrome (“delusion of doubles”, i.e. the belief that beloved ones had been replaced by impostors who bore a close physical resemblance to them) (Mace & Trimble 1991).[17] In rare cases, patients became criminal following neurosurgery. For example, a patient became severely sexually disinhibited immediately after thermocapsulotomy for OCD and was convicted of rape five months postoperatively (Rück et al. 2008).

It is important to note that personality changes caused by neurosurgical or other interventions in the brain cannot be reduced to psychogenic alterations that might be caused by fear of death, by the experience of disease or intensive therapy, or by psychosocial adjustment

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[17] The Capgras syndrome is supposed to be caused by a damage of connections from face-processing areas in the temporal lobe to the limbic system (Hirstein & Ramachandran 1997).

difficulties (e.g., the "burden of normality"; Gilbert 2012; Wilson et al. 2001). Rather these experiences can interfere with neurobiological changes in a complex manner.

Personality changes depend strongly on the localization and the extent of the lesion – be it caused by disease or by neurosurgery (Eslinger et al. 2004). Patients with prefrontal lesions (especially those with lesions involving the orbitoprefrontal and medial regions) are significantly impaired in both cognitive and affective empathy as compared to patients with parietal lesions and healthy controls (Shamay-Tsoory et al. 2004, n = 51). Patients with prefrontal lesions seem to produce an abnormally 'utilitarian' pattern of judgments on moral dilemmas; this could be attributed to diminished social emotion (Koenigs et al. 2007, n = 6).[18] Lesions to limbic and paralimbic structures can impair sexual drive, social attachment, and aggressiveness (Weissenberger et al. 2001). Lesions in various combinations of limbic structures, including the hypothalamus, can cause alterations in sexual behavior and sexual orientation (including hypersexuality and paraphilias) (Baird et al. 2007). Particularly damage to the orbitofrontal region of the limbic system can cause disinhibited (sexual) behavior. Lesions in the ventromedial PFC may deteriorate social conduct, decision-making and emotional processing (Tranel et al. 2002; Moll et al. 2005).[19]

Additionally, the age of lesion onset (e.g., prenatal, perinatal, early childhood, adolescence vs. adulthood onset) seems to determinate the psychosocial outcome (Eslinger et al. 2004; Trauner et al. 2001). Patients with early prefrontal cortex damage show a broad spectrum of cognitive, emotional, self-regulatory, and executive/metacognitive deficits that contribute to diverse developmental frontal lobe syndromes (Eslinger et al. 2004: review of 10 cases). Particularly, sexual deviation involving a deviation of the sexual object (e.g., pedophilia) seems to be associated with lesions prior to age 3 years (Baird et al. 2007). Furthermore, personality changes may depend on the cause of the lesion (e.g., hemorrhage vs. tumor resection) (Trauner et al. 2001).[20]

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[18] In the last years, patients with acquired psychopathy after lesions in the frontal lobes (particularly vmPFC and OFC) have come into the focus of the neuroscience of ethics; Phineas Gage has become its paradigm. Nevertheless, there seems to be a publication bias; since the prevalence of social and behavioral disorders after frontal lobe lesions is unknown, their causal relationship has not been sufficiently proven yet (Christen & Regard 2012).

[19] According to a lesion study, the right, but not the left vmPFC is a critical component of the neural systems that subserve social conduct, decision-making, and emotional processing (Tranel et al. 2002, n = 7).

[20] In contrast to several other studies, Trauner et al. (2001) did not find a difference between patients who had a pre- or perinatal focal lesion and control persons with regard to significant behavioral and emotional problems, if IQ was used as a covariate. But if IQ was not used as a covariate, significant differences were found between patients and controls with regard to behavioral, social, thought and attention problems. The authors propose different explanations for the disparity in findings between their study and those of others; particularly the cause of the lesion might be relevant: Whereas Trauner and colleagues investigated children and adolescents who had unilateral focal brain lesions from cerebral infarction or intraparenchymal hemorrhage, other studies have investigated patients who had lesions caused by brain tumors, tumor resections or brain traumata.

In the following, a short overview over personality changes after interventions in the brain, which are considered prima facie as negative or as positive, respectively, will be provided in order to prepare the ethical discussion of these interventions.

1.5 Negative personality changes after interventions in the brain

Many case studies report dramatic deteriorations of the patients' cognitive abilities, mood, personality, behavior or social functioning after interventions in the brain. The following paragraphs illustrate the spectrum of mental sequelae of different kinds of therapeutic interventions.

a) Brain tumor resection

Although cognitive dysfunctions following treatment for brain tumors (radiation, chemotherapy, and neurosurgery) are documented in many studies, it is difficult to estimate their prevalence. As most studies have not assessed the baseline functioning of participants before treatment, and due to the multimodal nature of brain tumor treatments, it is difficult to disentangle the influence of tumor and each specific treatment component. The impact of surgical resection of brain tumors on neurocognitive functioning is associated with the location of the lesion. Surgery to remove tumors in the cortical mantle affects functions coordinated by that area. Removing intratentorial tumors, too, can contribute to neurocognitive dysfunction, with documented impairments in working memory, sustained, selected and divided attention, organization and planning, and emotional control in children (De Luca et al. 2009).

Patients following brain surgery for tumor have higher degrees of emotional and social dysfunction compared to extra-cerebral neurosurgery patients and terminally ill cancer patients. Both tumor type and tumor location are significant influence factors for emotional and social dysfunctions including features such as anger, helplessness, fatigue, emotional dyscontrol, indifference, and maladaptive behavior (Andrewes et al. 2003, n = 69). Patients with lesions of the ventral frontal cortex or the temporoparietal cortex reported postoperatively significantly worse mood states (anxiety, depression, anger, irritability, fatigue) than did patients with other brain lesions (Irle et al. 1994, n = 141). Patients with bilateral (not with unilateral) surgical lesions of the orbitofrontal cortex showed impairments in social behavior and significant changes in their subjective emotional state (Hornak et al. 2003, n = 35). Furthermore, this group of patients was severely impaired at reward-related reversal learning (Hornak et al. 2004, n = 31).

Tumor resections from the frontal lobes can cause a lack of emotion and problems with decision-making, even in case of intact cognitive functions. In severe cases, psychopathy can develop which is characterized by impulsivity, antisocial behavior, and uncontrollable aggressions (Phineas Gage syndrome) (Damasio 1994; Eslinger & Damasio 1985; Eslinger et al. 2004; Meyers et al. 1992; Tranel et al. 2002, patient SB-2046).

Different behavioral disorders have been reported after surgery for frontolimbic tumors. For example, a patient developed kleptomania and compulsive gambling after removal of a craniopharyngioma; he became circumstantial and logorrheic, and displayed hypergraphia and a preoccupation with religious and moral ideas (Nyffeler & Regard 2001). Aggressive microsurgery for craniopharyngiomas in childhood has a significant impact on socio-emotional and behavioral functioning (Sands et al. 2005). A prospective study reports that the majority of children who had total resections of craniopharyngiomas were more or less severely affected by a hypothalamic syndrome which altered their social insertion and caused academic failure (Pierre-Kahn et al. 2005, n = 14). The high rates of intellectual impairment, poor social adaptation and emotional lability of craniopharyngioma survivors (30-60%) might be caused by an impaired frontal lobe function following surgery (Stelling et al. 1986).

Rarely, the resection of brain tumors can cause de novo psychiatric symptoms. For example, a patient with no previous mental illness developed major depression with psychosis after resection of a giant middle fossa hemangiopericytoma (Sade et al. 2006). Another patient developed a schizophreniform psychosis after excision and postoperative radiotherapy of an oligodendroglioma (Mace & Trimble 1991, Case C).

The spirituality of persons can be influenced specifically by the resection of brain tumors, too, whereby the localisation of the lesion is crucial: Tumor surgery on the occipitotemporo-parietal cortex but not on the frontotemporal cortex can significantly increase the personality trait ‘self-transcendence’ (an important component of spirituality) (Urgesi et al. 2010, n = 84).

Even tumor resections from brain areas, which have been considered recently as not relevant for cognitive capacities, personality, and behavior, can cause a wide spectrum of neuropsychological and behavioral abnormalities: Behavioral deficits or attention deficit problems were detected in 33% or 12.5%, respectively, of patients, who were operated for benign cerebellar tumors during childhood. Some of them demonstrated psychiatric symptoms such as mutism, addiction problems, anorexia, uncontrolled temper tantrums and phobia. The patients had difficulties in selective and, even more notably, sustained attention which resemble dysfunctions seen in patients with frontal lesions. There is evidence that cerebellar dysfunction includes a mild frontal dysfunction, explained by the cerebello-frontal connections (Steinlin et al. 2003, n = 24). The resection of benign cerebellar tumors causes in some children (28%) the Posterior Fossa Syndrome with the features mutism, oropharyngeal dyspraxia, emotional lability, different neuropsychiatric symptoms, and autistic behavior

(Catsman-Berrevoets & Aarsen 2010, n = 148). SPECT scan findings suggest that these impairments are secondary to supratentorial metabolic hypofunction following cerebellar surgery, maybe because of a functional disruption of the pathways connecting the cerebellum to the frontal areas of the cortex which are involved in planning and initiation of motor activities, including speech (ibid.).

b) Shunt placement for the treatment of hydrocephalus

After the placement of ventriculoperitoneal shunts for the treatment of hydrocephalus, two patients developed hypersexuality with inappropriate sexual behavior; this was supposedly caused by the septal damage due to the shunt placement (Gorman & Cummings 1992). Both lesions and stimulation of the septum have caused hypersexuality in animals and humans. The septum seems to be one locus of a circuit of structures mediating sexual behavior; further loci are the inferior frontal cortex, the hypothalamus and the amygdaloid nuclei (Gorman & Cummings 1992). Indeed, lesions in any of these regions have a major, site-specific impact on sexual behavior: Bilateral lesions of the amygdaloid nuclei produce hypersexuality (Klüver Bucy syndrome); whereas lesions in the hypothalamus reduce sexual activity (Gorman & Cummings 1992). This observation was the rationale behind treating sexual offenders with posterior hypothalamotomy (Freund 1980).

c) Pallidotomy for the treatment of Parkinsonism

A case of pedophilic behavior caused by right pallidotomy has been reported by Mendez and Shapira (2011): Their 59-year-old Parkinson patient underwent a right pallidotomy (lesion of parts of the globus pallidus). Immediately after the pallidotomy, he became markedly hypersexual. He forced his wife to have sex with him, masturbated frequently, propositioned his wife's female friends, hired strippers and prostitutes, and spent hours viewing Internet pornography. He was accused of touching his 5-year-old granddaughter inappropriately and asking her to touch his penis. He was ashamed of his behavior, complained of intrusive sexual thoughts and urges that overwhelmed him, and desired to just have his libidinal urges "normalized" again. The patient had no history of psychiatric illness, unusual sexual behavior, or drug-induced behavioral changes prior to his surgery. A reduction of his anti-PD medications resulted in a gradual decrease in his sexual behavior – but for the price of worsening of his Parkinsonism. A few further cases of disinhibition and inappropriate sexual behavior following pallidotomy have been published (Shannon et al. 1998: three cases persistent at 6 months; Dogali et al. 1995: one transient case). Cases of sexual disinhibition have also been reported as consequences of thermocapsulotomy or radiosurgery with high radiation doses (Rück et al. 2008).

d) Epilepsy surgery

After epilepsy surgery, heterogeneous cognitive, psychiatric and behavioral outcomes have been reported (reviews: Hamberger & Drake 2006; Macrodimitris et al. 2011; Spencer & Huh 2008; Téllez-Zenteno et al. 2007). Nevertheless, little information exists on long-term non-seizure outcome after epilepsy surgery (Hamberger & Drake 2006; Téllez-Zenteno et al. 2007). The vast majority of outcome studies do not even report the psychosocial outcome: A recent systematic review (Macrodimitris et al. 2011) has identified 5,061 articles related to epilepsy surgery of which only 68 (=1.3%) reported psychiatric outcomes.

The most important neurological sequelae after epilepsy surgery depend on the surgical technique and the lesion site: After anterior mesial temporal lobectomies, 0.4-4% of patients had partial hemianopsia, aphasia, motor deficit, sensory deficit or cranial nerve palsy; after neocortical resection, less than 10% of patients had de novo motor, visual, or cognitive deficits. After corpus callosotomies in adults, up to a third of patients developed mostly transient akinetic states or disconnection syndromes (consisting of mutism, ataxia, alexia, hemineglect, gait apraxia, and urinary incontinence); in rare cases, the alien-hand syndrome occurred (review: Spencer & Huh 2008).

The neuropsychological sequelae of epilepsy surgery depend significantly on the localization of the lesion, too: Frontal lobe resections lead to mild losses in psychomotor speed and motor coordination (Helmstaedter et al. 1998, n = 33). Whether a long-term memory decline occurs after epilepsy surgery, is reported inconsistently (reviews: Hamberger & Drake 2006; Téllez-Zenteno et al. 2007). Long-term memory decline may be associated with poor postoperative seizure control (Baxendale et al. 2012). Furthermore, the site of temporal lobe resection seems to affect the neuropsychiatric outcome: Significant decline in verbal memory occurs in 19-50% of patients who had dominant temporal resections (review: Spencer & Huh 2008). Several studies report a higher incidence of specific deficits of semantic functions after left than after right temporal lobectomy (Wilkins & Moscovitch 1978: selective impairment of semantic memory; Lu et al. 2002 and Tippett et al. 1996: category-specific naming deficits; Baxendale et al. 2012: impaired verbal learning; reviews: Hamberger & Drake 2006; Rausch 2002). In contrary, emotional learning seems to deteriorate more often after right versus left temporal lobe resections (Rausch 2002).

Although many papers report the improvement of psychiatric status after epilepsy surgery in the majority of patients (Blumer et al. 1998; Devinsky et al. 2005; Guangming et al. 2009; Guarnieri et al. 2005; Hannan et al. 2009; Hill et al. 1957; Jones et al. 2002; Lendt et al. 2000; Meldolesi et al. 2007; Taylor 1972; Wilson et al. 2005; Witt JA et al. 2008; reviews: Macrodimitris et al. 2011; Spencer & Huh 2008), the exacerbation or the onset of psychiatric disorders occurs after epilepsy surgery, too (e.g., Blumer et al. 1998; Devinsky et al. 2005; Guangming et al. 2009; Hill et al. 1957; Koch-Stoecker 2002; Mayanagi et al. 2001; Shaw et al. 2004; Siegel et al. 2008; Taylor 1972). One of the most feared complications of epilepsy surgery is psychosis; its overall postsurgical prevalence is 1-5% (Spencer & Huh 2008) and about 1% in patients without psychotic history (Calvet et al. 2011; Devinsky et al. 2005). Mace & Trimble (1991) report six cases of frank psychiatric illness after epilepsy surgery, including delusional depression, schizophrenia-like illnesses, and Capgras syndrome. More frequently reported are affective disorders, especially emotional lability and depression, which typically are transient (Calvet et al. 2011). The incidence of de novo affective disorders is 4-30% (review: Spencer & Huh 2008). The systematic review of Macrodimitris et al. (2011) reports prevalence rates of de novo depression from 4-18.2% and de novo anxiety from 6.9-13%. Postsurgical mood disturbances are often transient and usually occur in the first three months following surgery (review: Foong & Flugel 2007). De novo OCD and deterioration of behavior disorders of children following epilepsy surgery have been described in a few case reports (Foong & Flugel 2007). Changes in sexual behavior, typically hypersexuality, have been reported after temporal lobectomy, often together with depression, anxiety, and personality changes (Baird et al. 2002 and 2007; Hill et al. 1957). By way of example, a 14-year-old girl developed after selective amygdalohippocampectomy symptoms of excessive masturbation in inappropriate places, social withdrawal, irritability, aggressive behavior, crying spells and increasing depression (Ozmen et al. 2004). Several studies have reported that patients who have undergone amygdalotomy showed manifestations of hypersexuality and other symptoms of Kluver Bucy syndrome (Baird et al. 2007).

The psychiatric outcome after epilepsy surgery depends on several factors of which some are yet controversial. Most studies have found that seizure control is an important factor of the postoperative psychosocial outcome (e.g., Blumer et al. 1998; Koch-Stoecker 2002; Tanriverdi et al. 2008; Taylor 1972; Téllez-Zenteno et al. 2007; contrary findings: Shaw et al. 2004; Wrench et al. 2004; reviews: Foong & Flugel 2007; Macrodimitris et al. 2011; Spencer & Huh 2008). The role of the pre-operative personality has been established in several studies, too: A strong link exists between personality disorders and postsurgical psychiatric complications (Koch-Stoecker 2002). A schizotypal or schizoid compensated personality disorder might be a risk factor for postoperative psychosis (Calvet et al. 2011). The greatest predictor of postoperative depression is preoperative depression (Barbieri et al. 2011; Devinsky et al. 2005). High neuroticism and low extraversion seem to predispose to greater depression and disrupted family dynamics after surgery (Wilson et al. 2010). Further key factors for the psychiatric outcome seem to be the type and the localization of the lesion: The probability of postoperative psychosis seems to be increased for tumors, especially ganglioglioma (Koch-Stoecker 2002; Shaw et al. 2004). Patients with temporal resections have significantly higher levels of de novo depression, anxiety and psychosocial adjustment difficulties than extratemporal patients (Wrench et al. 2004). Lesions of the deeper temporal structures (e.g., uncus, hippocampal gyrus, hippocampus, and amygdaloid nucleus) may interfere with impulse control mechanisms; which is seen in the intensity, direction and fluctuation of the sexual drive and in the expression and control of the aggressive response to frustration (Hill et al. 1957). Furthermore, the size of surgical resection seems to be positively correlated with the occurrence of postoperative emotional lability (Anhoury et al. 2000). Finally, bilateral structural and functional abnormalities, particularly of the amygdala, could be a risk factor for postoperative psychoses (Shaw et al. 2004). However, many factors are not consistently associated with psychiatric sequelae, namely laterality of surgery, localisation of seizure focus, age at time of surgery, and continued auras (Spencer & Huh 2008).

e) Modern-day psychiatric neurosurgery

Psychiatric neurosurgery can have different negative mental side effects, whose rates seem due, at least partly, to differences in the volume of tissue lesioned (Greenberg et al. 2003). After capsulotomy, poor memory, loss of initiative, fatigue, apathy, aggressiveness, dysexecutive function behavior, and sexual disinhibition have been reported (Cosgrove & Rauch 1995; D'Astous et al. 2013; Dougherty et al. 2002; Feldman et al. 2001; Rück et al. 2008). Following subcaudatetractotomy, the development of undesirable personality traits has been reported in some patients (Feldman et al. 2001). After cingulotomy, transient mania and memory deficits have occurred (Feldman et al. 2001); one study reports a high suicide rate (12%) (Jenike et al. 1991).[21] After ventromedial frontal leukotomy, most patients with lesions in the ventral striatum (8 out of 11) developed substance dependence (Irle et al. 1998).

f) Deep brain stimulation

Although the clinical benefits of deep brain stimulation in the treatment of severe movement disorders, especially Parkinson's disease, dystonia and essential tremor, have been clearly proven, complex cognitive, affective and behavioral sequelae have been increasingly described and discussed (e.g., Bronstein et al. 2011; Christen et al. 2012; Hariz et al. 2006; Heo et al. 2008; Kirsch-Darrow et al. 2008; Kleiner-Fisman 2006; Kraemer 2013; Meagher et al. 2008; Morrison et al. 2000; Müller & Christen 2011; Parsons et al. 2006; Perozzo et al. 2001; Pillon 2002; Schneider et al. 2003; Schüpbach et al. 2006; Temel et al. 2005; Voon et al. 2006; Weaver et al. 2009; Witt K et al. 2008; Woods et al. 2006). DBS in the STN (the

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[21] Four out of 33 patients suffering from OCD and severe depression had committed suicide. The authors suppose that disappointment secondary to failure of this "last-resort" treatment has contributed to suicide.

most used target in Parkinsonian patients) causes sometimes mental and behavioral responses at the moment the stimulator is switched on or the stimulation parameters are modified. By way of example, acute stimulation of an electrode located in the STN using high stimulation parameters (50% higher than therapeutic) induced funny associations, leading to infectious laughter and hilarity in two patients (Krack et al. 2001). In some cases, acute stimulation has caused aggressive behavior: One patient showed aggressive outbursts during intra-operative test stimulation (Bejjani et al. 2002).[22] Another patient showed spontaneous, unprovoked aggressive outburst, which were clearly related to the stimulation (Sensi et al. 2004). Also transient acute depression has been reported that occurred when stimulation was delivered to the left substantia nigra, 2 mm below the site where stimulation alleviated the signs of Parkinson's disease (Bejjani et al. 1999).[23]

DBS in the STN can cause long-lasting mental changes and even changes in personality: A meta-analysis of 82 studies with 1,398 Parkinsonian patients has shown that cognitive deteriorations occurred in 41%, depressions in 8%, mania, aggressiveness or changes in personality in 0.5% (Temel et al. 2006). The suicide rate in the first postoperative year is 13 to 16 times higher than in a population matched by age, gender, and habitation (Voon et al. 2008: meta-analysis with 5,311 patients). Forty case studies (until 2009) report incidences of aggression, delusion, depression, suicides, hallucinations, hypersexuality, hypomania, or mania after STN DBS (Christen & Müller 2011). Patients who developed (hypo)mania after DBS of the STN or GPi showed impaired judgment (Herzog et al. 2003), loss of normal social inhibitions (Herzog et al. 2003), unrestrained buying (Herzog et al. 2003; Leentjes et al. 2004; Mandat et al. 2006; Romito et al. 2002; Lilleeng & Dietrichs 2008), kleptomania (Sensi et al. 2004), venturesome dealings, reckless car-driving (Leentjes et al. 2004; Romito et al. 2002), sexual harassment (Romito et al. 2002), hypersexuality (Doshi & Bhargava 2008; Houeto et al. 2002; Krause et al. 2001; Roane et al. 2002; Romito et al. 2002), love delusion (Herzog et al. 2003), exhibitionism or sex tourism (Houeto et al. 2002).

Affective and social problems, especially in partnership and work, occur during STN DBS often in spite of a good clinical outcome (Brentrup et al. 2004; Gisquet 2008; Houeto et al. 2002; Krause et al. 2001; Leentjes et al. 2004; Northoff 2001; Perozzo et al. 2001; Romito et al. 2002; Schüpbach et al. 2006; Sensi et al. 2004). Familial and professional difficulties

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[22] The electrode responsible for the aggressive burst was located in the triangle of Sano between the medial STN and the posteriomedial hypothalamic region, which used to be selectively lesioned to treat medically intractable aggressive behaviors in severely affected psychiatric patients.

[23] Acute stimulation effects have also been reported in psychiatric DBS: Stimulation of the VC/VS-NAcc region has been associated with acute induction of elevated mood, to the point of hypomania, or of panic attacks, respectively. In all reported cases, the undesirable effects of DBS on mood were reversible with changes in stimulation parameters (review: Goodman & Alterman 2012).

develop partly because of psychiatric disorders, partly because of a hedonistic re-orientation of the patients (Gisquet 2008; Schüpbach et al. 2006).

Even the ability for social-moral judgment is significantly deteriorated in some patients under STN DBS: Bothe and colleagues report that 2 out of 15 patients were socially maladjusted after STN DBS for more than one year. Under DBS, their power of sociomoral judgment (measured with the 6-level Kohlberg scale; Kohlberg 1984) decreased from level 4 (adhering to social system and conscience) to level 2 (serving one's own interests and letting others do the same). This effect was reversible when the stimulation was switched off (Bothe 2003; Brentrup et al. 2004).

Whether DBS will cause cognitive, affective, or behavioral sequelae is not predictable for a given patient. This depends not only on the patient's personality and psychiatric history, but also on several technical parameters, in particular the target of the electrodes (STN, GPi, Vim, or PPN) (Temel et al. 2006; Krack et al. 2010). Cognitive and affective side effects occur more frequently after stimulation of the STN (Hariz et al. 2008); this is understandable, as the STN is part of various thalamo-cortical circuits (Marani et al. 2008). In case of STN DBS, the occurrence of mental sequelae also depends on the exact localization of the electrodes within the target (Cakmakli et al. 2009; Shin-Yuan et al. 2004; Tsai et al. 2007), the selection of electrode contacts (Kulisevski et al. 2002; Tommasi et al. 2008), and the stimulation parameters (frequency, pulse width, and amplitude) (Krack et al. 2001; Raucher-Chéné et al. 2008; Smeding et al. 2007; Ulla et al. 2006). Not only STN DBS may cause mood or behavior disorders: Also a dystonia patient developed depression, psychotic symptoms, and heightened pain perception following DBS of the GPi; the cause was a dislodged electrode so that the left amygdaloid region was stimulated (Piacentini et al. 2008).

After DBS for psychiatric disorders, adverse mental effects have been reported, too:

OCD: A patient treated with ALIC DBS developed hypersexuality and hypomania and finally suicidal ideations because the hypersexuality came into conflict with his conservative Christian belief (Chang et al. 2010). Another patient developed a manic episode with phases of child-like affect and hyperreligious speech following NAcc DBS (Haq et al. 2010). Transient hypomania occurred in 50% to 60% of patients treated with ALIC-NAcc DBS (De Koning et al. 2011). Following VC/VS stimulation, a case of hypomania was reported (Greenberg et al. 2010); and following STN stimulation, 4 out of 16 patients suffered from transient psychiatric side effects (hypomanic status with irritability and impulsivity, anxiety and manic symptoms with euphoria, depressive symptoms, or obsessions, respectively) (Mallet et al. 2008).

Major depressive disorder: Two out of 15 patients, who were treated with VC/VS DBS, developed hypomania or a mixed-bipolar state and 5 an increased depression, partly with suicidality (Malone et al. 2009). Following NAcc DBS, 2 out of 10 patients either attempted or committed suicide; both events were not related to parameter changes, and both patients had attempted suicide previous to DBS (Bewernick et al. 2010).

Tourette's syndrome: Following DBS of the NAcc, a patient developed major depression and attempted suicide four years later (Müller-Vahl 2013).

Obesity: A patient who was treated with stimulation of the fornix for severe obesity developed flights of ideas and a severe sleep disorder (Hamani et al. 2008).

Nowadays, side effects of DBS are investigated extensively and in a sophisticated manner. But although our in-depth analysis of scientific journal papers on STN DBS has found a well-developed sensibility for DBS side effects in the DBS community, the side effects are not yet measured and evaluated sufficiently (Christen & Müller 2011; Christen et al. 2012). Most of the studies are retrospective, have too small numbers of cases, too short follow-up times, no control groups, no randomization and no blinding. The majority of methods used investigate subtle cognitive changes which may be statistically significant but whose relevance for the patients is unclear. Only a minority of investigations focus on self-assessments of patients and even less on assessments of the patients' caregivers. This methodological bias implies unawareness for certain psychosocial side effects (Christen et al. 2012). In spite of these deficits, DBS research is exemplary for neurosurgery with regard to the awareness for mental side effects.

1.6 Positive personality changes after interventions in the brain

Interventions in the brain do not necessarily deteriorate mental properties or the personality. In some cases, it is even justified to speak of psychotherapy via scalpel.

a) Brain tumor treatments

A meanwhile well-known case may illustrate how severe negative personality changes were caused by a brain tumor and how brain surgery "restored" the personality: A 40-year-old married school teacher became obsessed with child pornography and started to solicit prostitutes and to molest his stepdaughter. His wife evicted him from the family home after discovering his sexual advances to her daughter. He was accused and found guilty by the court of child molestation. He had to enter a treatment programme for convicted sexual offenders. But since even there he was continuously asking women for sex, he was expelled from the programme. One day before he was due to go to prison, he went to hospital because of a headache and indomitable sex drive. A MRI scan revealed that he had an egg-sized brain tumor in the frontal lobe – an area essential for judgment, social behavior, and self-control. The tumor had yet infiltrated the hypothalamus which also controls the sexual drive. After tumor resection, the pedophiliac drive vanished completely, and the man went home to his family. But several months later, he secretly started to collect pornography again. A MRI scan showed that the tumor had re-grown. It was removed once more, and the abnormal sexual drive vanished again (Burns & Swerdlow 2003).

This rare case is a paradigm for how a brain disease causes a personality disorder and aberrant behavior, and how an efficient treatment of the disease literally cures the personality and the behavior. But although this case is rare insofar the causal relationship between brain disease and personality disorder is obvious, it is no exception.

In a retrospective review of cases with benign or malignant *frontal or temporolimbic tumors* that caused psychiatric symptoms, 7 out of 8 patients were substantially improved or cured after neurosurgery, irradiation or chemotherapy. By way of example, a patient had been, in departure from his previous personality, apathetic and irritable; he also suffered from anomia and hemiparesis. Two months after treatment of a malignant small-cell neoplasm with cranial irradiation and chemotherapy, the patient's personality change had resolved considerably, while the mass lesion showed a dramatic resolution. Another patient who had developed profound depression, a severe weight loss and hemiparesis, reported substantial lessening of his depressive symptoms after resection of a metastatic carcinoma from the right frontal lobe (Filley & Kleinschmidt-DeMasters 1995). The removal of temporal lobe tumors from two pediatric patients with histories of seizures and unusually aggressive and antisocial behavior made them not only seizure-free, but also reduced their aggressive behavior markedly (Nakajii et al. 2003).

These and other case studies document that treatments (resections, irradiation, and chemotherapy) of frontal or temporolimbic tumors do not necessarily corrupt the personality of patients, but may restore the pre-morbid personality.

b) Epilepsy surgery

Suchlike positive consequences of neurosurgery are known in particular for patients suffering from epilepsy. These patients have a significant higher prevalence of lifetime psychiatric disorders (35%) than the general population (20.7%) (Téllez-Zenteno et al. 2007); particular high are the rates in patients with temporal lobe epilepsy (Foong & Flugel 2007). Furthermore, anti-epileptic medications may contribute to depression and anxiety (Foong & Flugel 2007). Therefore it can principally be expected that a successful surgical treatment of epilepsy might also be a cure of psychiatric comorbidities.

In patients with intractable temporal lobe epilepsy, temporal lobectomy improves, on average, cognitive functions of the contralateral hemisphere by preventing the propagation of epileptic discharge to other brain areas and by giving advantage to previously suppressed capacities in extratemporal areas (Shin et al. 2009, n = 54; see also Helmstaedter et al. 1998, n = 45). Some studies even report improvements in verbal memory and full-scale IQ after non-dominant temporal lobectomies (review: Spencer & Huh 2008).

After surgery for refractory epilepsy, positive personality changes seem to outweigh negative ones (Blumer et al. 1998; Guangming et al. 2009; Hannan et al. 2009; Hill et al. 1957; Lendt et al. 2000; Meldosi et al. 2007; Taylor 1972; systematic review: Macrodimitris et al. 2011), although these are not the primary goal of intervention, but freedom of seizures. Mainly depressions, anxiety, behavioral disorders and severe obsessive-compulsive disorders are often improved (Devinsky et al. 2005; Guangming et al. 2009; Guarnieri et al. 2005; Hannan et al. 2009; Lendt et al. 2000; Witt JA et al. 2008; review: Foong & Flugel 2007). In a series of 100 patients who had temporal lobe surgery, aggressiveness was most noticeably reduced, and those who improved came largely from the preoperatively psychopathic group (Taylor 1972). Improvements in aggressive behavior in children following surgery for temporal lobe epilepsy have been reported in several papers (review: Foong & Flugel 2007). In a few cases, epilepsy with fetishism was relieved by temporal lobectomy (Hunter et al. 1963; Mitchell et al. 1954; see also Hill et al. 1957). In some cases, this intervention restored normal sexual functioning (review: Baird et al. 2007). In many patients increased warmth in social relationships and a lessening of egotism have been described (Hill et al. 1957).

The mechanism by which psychiatric disorders improve after epilepsy surgery is not well understood; whether the improvements result from reduction or elimination of seizures and interictal epileptiform activity or other effects is unclear. However, better seizure outcomes seems to predict improvement in psychiatric status (Blumer et al. 1998; Devinsky et al. 2005; Spencer & Huh 2008; Tanriverdi et al. 2008; Witt JA et al. 2008; reviews: Spencer & Huh 2008; Téllez-Zenteno et al. 2007). Furthermore, improved sense of self-control, reduced fear of seizures, greater activity levels, and reduced burden of anti-epileptic drugs may also be important (Devinsky et al. 2005). A longitudinal follow-up study of psychosocial outcome trajectories following anterior temporal lobectomy suggests that a complex relationship exists between psychosocial adjustment and seizure freedom, rather than a simple positive linear relationship (Wilson et al. 2005, n = 89).

Only relatively few long-term controlled studies of actual lifetime performance after epilepsy surgery exist. Because of a lack of appropriate control groups it is difficult to characterize the impact of surgery. A recent controlled study found that the vast majority

(68%) of the temporal lobectomy surgery group exhibited improved psychosocial status compared with 5% of the medical management group. Surgery had a significant positive impact on employment, independent living, driving and financial independence (Jones et al. 2002, $n_{\text{lobectomy}} = 61$, $n_{\text{medical}} = 23$). Nevertheless, epilepsy surgery seems to improve vocational status only modestly (review: Spencer & Huh 2008). In children, the most notable improvements after epilepsy surgery are less hyperactivity, greater emotional well-being and better socialisation (review: Spencer & Huh 2008).

c) Resection of arachnoid cysts

Even the resection of arachnoid cysts can be a cure for certain psychiatric illnesses and personality disorders, although it is recommended only if neurological symptoms or signs of increased intracranial pressure are present. But since the prevalence of arachnoid cysts is considerably increased in psychiatric patients, a causal relationship between arachnoid cysts and certain psychiatric disorders is supposable. Based on this hypothesis, two patients with a slow onset personality disorder, who suffered from so-called asymptomatic arachnoid cysts, underwent neurosurgery, although they did not initially appear to fulfill the established criteria for organic personality disorders either according to ICD-10 or DSM-IV. Both patients showed considerable improvement or even remission of psychopathology after the resection of the arachnoid cysts, also over the long-term catamnesis. Therefore, Karl Bechter and colleagues recommend neurosurgery when therapy-resistant psychiatric disorders are observed in patients with arachnoid cysts (Bechter et al. 2010). Certainly, this hypothesis needs further research for investigating a possible causal relationship between arachnoid cysts and psychiatric disorders.

d) Modern-day psychiatric neurosurgery

After neurosurgery for psychiatric disorders (especially for OCD and depression), positive changes in personality have been observed frequently, e.g., lesser degrees of neuroticism, anxiety, depression, dependence, and obsessionality, a greater depth of feelings, a more sociable behavior and an improved capacity for pleasure (Sachdev & Hay 1995). Stereotactic anterior cingulotomy has been reported to be effective for 30-70% of patients with intractable major depression, OCD, or anxiety disorders (Ballantine et al. 1987; D'Astous et al. 2013; Dougherty et al. 2002; Jenike et al. 1991; Jung et al. 2006; Kim et al. 2003; Spangler et al. 1996; reviews: Cosgrove & Rauch 2003; Feldman et al. 2001). The effectiveness of subcaudatetractotomy (with implantation of radioactive rods) has been confirmed by multiple studies (review: Feldman et al. 2001). It allowed 40-60% of the patients with affective disorders to live normal or near-normal lives and reduced significantly the suicide rate

(Bridges et al. 1994). Lesional procedures offer benefit to about 35%-70% of patients with intractable OCD and depression (review: Greenberg et al. 2003).

Positive changes have also been reported for the neurosurgical treatment of (auto-) aggressive behavioral disorders: In an adolescent boy with Tourette's syndrome and severe self-injurious behavior, cingulotomy and subsequently limbic leucotomy reduced the severity and frequency of his self-injurious behavior (Anandan et al. 2004). Sexually delinquent men, who had undergone stereotactic hypothalamotomy for the treatment of their extreme sexual aggressiveness, showed constant modifications postoperatively: less domination by sexual drive, less self-centredness, aggressiveness, and impulsivity, increased openness, self-criticism, and inner harmony, and a marked consolidation of their social interactions and occupational situation (Dieckmann et al. 1988, n = 8).[24] Also stereotactic amygdalotomy can be an effective treatment for severe aggressive behavioral disorders. Over a thousand cases have been studied (Langevin 2012). A review about 13 clinical studies reports that post-operative improvement in aggressive behavior varied between 33% and 100% (Mpakopoulou et al. 2008). The authors recommend this treatment for carefully selected patients with medically refractory aggressive behavioral disorders; Fountas et al. (2007) recommend it for severe, treatment-refractory cases of self-mutilation disorder. On the other side, the amygdala has a critical role of in fear conditioning (Langevin 2012), and therefore an indispensable role in promoting survival by compelling the individual away from danger (Feinstein et al. 2011).[25] Furthermore, the amygdala has an important role in sexual functions (Baird et al. 2007). Therefore, an amygdalotomy is a two-sided weapon: it might be a cure for non-adaptive fear, but the evolutionary value of fear could be lost, too, and the price for "taming" might be hypersexuality.

e) Deep brain stimulation

DBS of the STN allows for a significant reduction of levodopa for most Parkinsonian patients; consequently it reduces medication-induced side effects effectively and sustainably. This is valid not only for dyskinesia and other levodopa-related motor complications (Deuschl et al. 2006; Hamani et al. 2005; Weaver et al. 2009), but also for psychiatric side effects of the drugs. Under DBS, the dopamine dysregulation syndrome (Dodd et al. 2005) or the "hedonistic homeostatic dysregulation" (Voon et al. 2006) with impulse control disorder, such

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[24] The paper does not mention whether the patients gave their informed consent, and whether they were living in jail or in forensic institutions at the time of neurosurgery.

[25] Lesioning studies with Vietnam veterans have highlighted the central role of the amygdalae in the patho-physiology of post-traumatic stress disorder (PTSD) (Koenigs et al. 2008). It is known from experiments with amygdala-lesioned monkeys as well as from a case study of a patient suffering from the Urbach-Wiethe disease (a condition that causes a nearly complete bilateral destruction of the amygdalae) that the loss of the amygdalae causes a lack of avoidance and caution (Feinstein et al. 2011). Damage to the amygdalae seems to cause specific deficits comprising the recognition of the emotion of fear (Adolphs et al. 1994; Sprengelmeyer et al. 1999).

as pathological gambling, addiction to levodopa, and hypersexuality, can disappear. Insofar, DBS of the STN and the subsequent reduction of the dopaminergic drugs are in some cases an unintended cure for impulsive control disorders, especially for pathological gambling and hypersexuality (Eusebio et al. 2013; reviews: Broen et al. 2011; Demetriades et al. 2011). Furthermore, several papers report enhanced affective and cognitive functioning following DBS of the STN (e.g., Ardouin et al. 1999; Northoff 2001; Schneider et al. 2003).

DBS for the treatment of psychiatric disorders has positive effects in many patients insofar as it reduces the symptoms of a treatment-resistant psychiatric disease. For example, in patients with treatment-resistant OCD, the average overall responder rate is about 50% (review: De Koning et al. 2011).[26] In patients with treatment-resistant major depressive disorder, response rates were 33-92% (review: Anderson et al. 2012; additionally: Schläpfer et al. 2013). In some patients not only the disorder addressed by DBS responded or remitted, but also a comorbid disorder resolved (e.g., depression or addiction); sometimes a comorbid disorder resolved, although the addressed disorder did not respond (Krack et al. 2010; Kuhn et al. 2007 and 2009a; Mantione et al. 2010; review: De Koning et al. 2011).

1.7 Incidence and relevance of personality changes caused by neurosurgery

The above presented clinical studies and case studies shed light on the broad spectrum of cognitive, affective, and behavioral changes and personality changes, that may occur after neurosurgical interventions. However, both the incidence and the relevance of mental changes caused by interventions in the brain is an issue of controversy in medicine. Whereas some neurosurgeons think that generally each brain surgery bears a certain risk for changes of cognitive capabilities or affective properties, others hold this true only for a few special cases. Consensus exists only for interventions in brain areas which are doubtlessly involved in the control of cognitive or affective functions, e.g., the frontal cortex and the limbic system. But although the brain can be modeled as a modular system, it is more and more recognized as a greatly interconnected network system, in which higher emotional and cognitive functions are based on more fundamental functions (Damasio 1994; Gainotti 2001; Schmahmann 2010). Particularly, the cerebellum was formerly thought to be involved only in motor activities; nowadays, there are converging evidence that cerebellar circuitry contributes to the regulation of language, verbal memory, spatial tasks, executive functions and emotions (Grimaldi & Manto 2012). Another example for the tight connection of motor and non-motor functions is the fact that movement abnormalities and behavioral symptoms commonly occur together in

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[26] Depending on the study and the selected target, the response rates (at least 35% reduction on the Yale-Brown Obsessive Compulsive Scale) after one year of chronic stimulation vary between 10% (Huff et al. 2010, NAcc) and 100% (Jimenez-Ponce et al. 2009, ITP).

diseases of the basal ganglia; this can be explained by the anatomic and neurochemical connections between the basal ganglia and the limbic system (Skuster et al. 1992). Therefore a strict separation of personality-relevant and personality-neutral brain areas is not justified. Particularly the neural mechanisms of moral cognition are not restricted to the prefrontal cortex, limbic areas or any other brain region; in fact they emerge from the integration of context- and content-dependent representations in cortical-limbic networks. This integrative model is supported both by lesion studies and functional imaging (Moll et al. 2005). Furthermore, each brain surgery bears a risk of complications, e.g., bleedings, liquor accumulation, swelling, or inflammation. Therefore, the risk of personality changes should be taken into account for *all* neurosurgical interventions in the brain (Müller S 2007; Merkel et al. 2007, p. 6).

The controversy about the incidence and the relevance of mental changes and personality alterations caused by interventions into the brain has several reasons:

1) The understanding of the brain is still fragmentary. For most interventions it is not fully understood why they cause certain mental effects. A comprehensive model of the brain has not been developed until now; thus most new interventions are developed on the basis of ad hoc hypotheses and trial-and-error approaches.

2) Research on mental disorders and personality changes caused by interventions in the brain is meager. Most neurosurgical studies report mortality statistics and surgery-related neurological disorders. Not since a few years, (health-related) quality of life (HRQOL or QoL, respectively) is investigated in a number of neurosurgical studies, too. Nevertheless, this is at best an indirect measure for certain mental disorders. Furthermore, the clinical usefulness of HRQOL measures, which average across both good and poor outcomes, has to be questioned, since an average measure of outcome provides limited clues about the expectable outcome of particular patients (Wilson et al. 2005).

3) For diagnosing and evaluating personality changes, medicine depends on the psychological personality research — a heterogeneous field of research, which contains a multitude of concepts of “personality”, “personality trait”, and “change in personality”.

4) Methodological difficulties exacerbate the determination of the incidence of personality changes caused by interventions in the brain: Sequelae of brain diseases, medication, surgery, and radiation are difficult to differentiate. Furthermore, the impact of some side effects on the patient’s life is hard to determine, especially in comparison with the impact of the effects of the disease’s natural progression. Additionally, for some mental disorders no objective measurement tools are available. In certain cases even severe behavioral disorders are not captured by standard psychological tests and personality inventories. This is valid for example

for psychopathy in the context of a frontal brain syndrome (Brower & Price 2001; Damasio 1994; Gainotti 2001). Particularly tests for the moral cognition lack ecological validity; the making of moral judgments on classic moral dilemmas does not tell much about everyday moral reasoning (Moll et al. 2005). Furthermore, patients, their social surrounding, and their physicians sometimes valuate certain changes in personality quite differently. This holds true especially for hypomania, increased energy, novelty seeking, risk willingness and sexual drive. Therefore, the ethical assessment of interventions in the brain has to reflect complex methodological difficulties. To deal with them, Markus Christen and I have introduced an analytic scheme that classifies therapy side effects along two gradual, qualitatively described dimensions: (1) measurement complexity of the side effect, and (2) relative life impact of the side effect (i.e., life impact of the side effect weighted by its incidence in the natural disease history) (Müller & Christen 2011; see Chapter 4).

5) Not much is known about the social sequelae of interventions in the brain, although they are frequent and often severely impact the patients' lives. Many patients have to change their profession or become even incapable of work. Reasons for that can be acute or long-term cognitive sequelae (e.g., reduced attention or concentration, poor memory, word finding difficulties) or affective disorders (e.g., difficulties to control negative emotions as anger and fear). But also a change to a more hedonistic thinking or a decreased social conformance (as observed in some DBS patients) can cause professional failure. Negative sequelae of interventions in the brain have been reported also for partnerships and familial lives (e.g., divorce) (Schüpbach et al. 2006). One important reason for this can be the "burden of normality", i.e., a psychosocial syndrome which comprises problems of adjustment, when chronically ill patients have to learn to become well (Gilbert 2012; Wilson et al. 2001). On the other hand, some patients are confronted with severe legal consequences because of certain deficits or behavioral disorders after interventions in their brains (e.g., loss of the driving license). In spite of the significance of suchlike psychosocial sequelae, only a handful of studies address social, familial, professional, and financial consequences of brain interventions.

6) Subtle, but existential consequences as changes of the self-perception or the experience of personal identity cannot be measured with the tools available; therefore they are systematically underestimated.

1.8 Ethical debate about neurosurgery

Bioethics has not paid much attention to neurosurgery until now – apart from a few exceptions. The most important exception is DBS for treating psychiatric disorders. Since its very begin, it has been accompanied by an intensive ethical debate (e.g., Bell et al. 2009; Dunna 2011; Fins 2009; Greenberg & Rezai 2003; Hall & Carter 2011; Mathews et al. 2011; Pacholczyk 2011; Rabins et al. 2009; Synofzik & Clausen 2011; Synofzik & Schläpfer 2008; Woopen et al. 2012 and 2013). This imbalance of ethical concern contrasts with the overall number of DBS patients (> 100,000)[27] compared to about 200 psychiatric DBS patients (until 2013). Furthermore, it disregards the entanglement of motor functions, cognition, mood and behavior affected by both Parkinson's disease and all pharmaceutical and neurosurgical treatments. Particularly, epilepsy surgery has been severely neglected by bioethicists.

The reason for the biased bioethical concern in relation to the clinical relevance of the issues may be that attempts to manipulate directly the mind by technical means are considered being theoretically and ethically more challenging than therapies which might accidentally or fatefully cause mental changes. Additionally, the history of psychosurgery raises major ethical issues against upcoming methods to treat psychiatric disorders by neurosurgery.

The delayed start of the bioethical debate about neurosurgery assumedly has several reasons: Firstly, decisions in neurosurgery are often very complex even from a mere medical point of view and very individual. Secondly, changes in personality after brain surgery used to be seen as fateful events.

Indeed decisions about an intervention in the brain can be conceptualized as neurosurgical dilemmas, in which possible benefits and adverse effects have to be balanced. For example, the decision about the resection of craniopharyngiomas in childhood has been described as a "surgical dilemma" (Dhellemmes & Vinchon 2006), since surgeons have to choose between radical tumor resection and the occurrence of postoperative cognitive and endocrine deficiencies (including memory loss, cognitive deficits, behavioral problems, and psychiatric disorders). But regarding decisions about interventions in the brain as a mere medical issue, is less and less justified for several reasons:

Firstly, the decision about a brain intervention can imply an ethical dilemma, too, if two conflicting values have to be balanced, for example life expectancy versus quality of life or versus saving sensory functions or cognitive capacities (Müller S 2007). Particularly, the decision about DBS parameters can involve a dilemma, for example if good motor functioning can be realized only for the price of mental health.[28]

Secondly, many brain surgeries are nowadays actually elective interventions. This holds especially for interventions for which alternative treatment options exist, which have lesser risks for personality changes (e.g., radiosurgery for small to medium-sized brain tumors) or for which a wait-and-watch strategy is justified (e.g., for some arteriovascular malformations).

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[27] www.medtronicdbs.com/parkinsons/about/benefits-and-safety/index.htm (accessed: 07.02.2014).

[28] Such a case has been described by Leentjes et al. (2004).

Therefore, neurosurgically caused personality changes can be considered less and less as fateful events.

Anyway, the more microsurgical interventions in the brain become one out of several options, the more important becomes the systematic and careful research on risks and side effects of all options available. This is necessary, since in case of elective interventions, patients have a higher claim for information about all risks and side effects than in case of medically compulsive interventions. The ethical issues of neurosurgery are the more explosive the less compulsive a given neurosurgical intervention is.

Thirdly, the rapidly grown possibilities to intervene very precisely into the brain and to modify exactly very specific functions allow for modifying a given personality specifically, even with the aim of enhancement.

For these reasons, interventions in the brain require not only medical considerations, but also value-based decisions. Thus interventions in the brain have to be reflected from an ethical point of view, too.

The following chapters investigate ethical issues of different treatment options (magnetic fluid hyperthermia therapy, microsurgery, radiosurgery, radiation therapy, deep brain stimulation) for different brain diseases (malignant brain tumors, vestibular schwannomas, Parkinson’s disease, psychiatric disorders) which can impact the patient’s personality or capability for autonomy.

2. Magnetic fluid hyperthermia therapy for malignant brain tumors – An ethical discussion

This chapter investigates the nanoparticle-based Magnetic Fluid Hyperthermia (MFH) therapy of malignant brain tumors, particularly of glioblastoma multiforme, according to the principles of the biomedical ethics of Beauchamp and Childress.

The diagnosis of glioblastoma multiforme is not only a highly probable prediction of death within the next 15 months, but also a prognosis of probably radical and rapid changes in personality, since these highly aggressive tumors often affect the temporal and frontal lobes. Since the disease can destroy the physical basis of understanding, rational thinking, socio-moral judging, controlling actions, and language, the patient's capability of autonomous decision-making is at stake. The only question is whether the patient will die before the disease will destroy his/her personality and capability for autonomy or afterwards. Since malignant brain tumors pose a manifest threat to the patient's capability for autonomy, respect for the patients' autonomy is realized first of all in saving their brain functions. This disease is a paradigm for the argument that not only interventions in the brain, but also their waiving can be ethically problematic. Furthermore, it supports paradigmatically the understanding of the principle of respect for autonomy in terms of saving the patient's capability for autonomy, if it is endangered by disease.

Preliminary results of MFH therapy have shown evidence of a local effectiveness and only minor to moderate therapy-associated side effects. Since the MFH therapy may slow down tumor growth and diminish tumor volume, it offers the chance to save or restore the patient's personality and capability of autonomy. Therefore I recommend the further development of this therapy and argue against a moratorium for nanomedicine based on general ethical or political concerns against nanotechnology.

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Magnetic fluid hyperthermia therapy for malignant brain tumors – an ethical discussion.

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Final Remark

Since May 2010, the magnetic fluid hyperthermia therapy (MFH) developed by MagForce has an official approval throughout Europe for the treatment of brain tumors.[1] In the meantime, the results of a phase II study have been published (Maier-Hauff et al. 2011), which reinforce the positive evaluation of the MFH therapy for treating glioblastoma multiforme. In this single-arm study in two centers, 59 patients suffering from recurrent glioblastoma multiforme had been treated with MFH therapy and fractionated stereotactic radiotherapy. The treatment led to a significantly prolonged overall survival following diagnosis of first tumor recurrence (OS-2): The median OS-2 of the study participants was 13.4 months compared to 6.2 months in a recent study with the current standard therapy (including the use of temozolomide); this is a significant extension of the median overall survival following diagnosis of first tumor recurrence. The majority of the gain in overall survival following reoccurrence can be attributed to thermotherapy plus radiotherapy. Except for worsening of hemiparesis, no prolonged adverse effects were observed. Unfortunately, the paper does not report data of the psychiatric outcome and of quality of life; to investigate these outcome parameters is recommendable for future studies.

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[1] www.magforce.de/fileadmin/magforce/3_studien/Update_patient_information/Questions_and_Answers.pdf (assessed: 06.02.2014).

3. Decision-making of vestibular schwannoma patients

This chapter investigates the decision-making of patients suffering from vestibular schwannomas (acoustic neuromas). These benign, slowly growing tumors cause several neurological disorders (loss of hearing, imbalance, vertigo, facial paralysis, and trigeminal pain) and finally death, but they generally do not compromise the cognitive abilities or the personality. Nevertheless, the latter may happen after tumor resection: In a significant proportion of neurosurgically treated patients neuropsychological impairments, depression, or mild personality changes occur. Some patients become incapable of work and dependent on help. Therefore, this disease is an example for an ethical dilemma in neurosurgery.

Nowadays, alternative treatments, namely radiosurgery (e.g., Gamma Knife or Cyber-Knife) and fractionated radiotherapy are available, which have comparable tumor control rates but lesser side effects than tumor resections. Especially physical functioning, mental health, and the social, professional and financial situation are significantly better for patients who had received radiosurgery or radiotherapy than for surgically treated patients. Nevertheless, the comparison of the different therapy options is complex even from a mere medical perspective, and it is difficult to justify the superiority of an option in general. The situation is complicated by the fact that the patients' evaluations of the different therapy options are based on different personal values (e.g., independence, working capacity) and fears (fear of personality change after neurosurgery, fear of radiation, or fear of tumor recurrence).

The aim of the following study was to investigate the decision-making of vestibular schwannoma patients. Not only the medical consultation, but also further influences on the patients' therapy decisions were investigated. The study is based on a postal questionnaire survey of vestibular schwannoma patients in Germany. Responses of 739 patients were received (survey response rate: 78%). The survey reveals that radiosurgery and radiotherapy are withheld from the vast majority of vestibular schwannoma patients through a unilateral medical counseling. Furthermore, information about side effects was usually insufficient, especially with regard to more subtle sequelae as depressions, headaches, impairments of the physical condition or of mental health – although these side-effects are not only common, but also evaluated as severe sequelae by patients. In order to overcome these shortcomings we recommend to advice all patients on all therapy options by an interdisciplinary team. The counseling should firstly be based on evidence-based information and secondly respond to the patients' individual life situation and preferences.

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4. Deep Brain Stimulation in Parkinsonian patients – Ethical evaluation of stimulation-induced personality changes

This chapter investigates ethical issues of deep brain stimulation of the nucleus subthalamicus (STN DBS) for Parkinsonian patients. Whereas its beneficial effects on motor functions are well established, cognitive, affective and behavioral sequelae come increasingly into the focus of clinical research. The ethical analysis is based on a comprehensive literature analysis of the research literature on STN DBS, which covers 66 case reports, 69 review papers, and 347 outcome studies from 1993 to 2009.

In order to evaluate whether the side effects may counteract the beneficial effects of STN DBS, Markus Christen and I have considered particularly the difficulties of identifying affective, behavioral and social sequelae of DBS and of differentiating between disease-related and therapy-induced effects. Then we have classified the different side effects reported in literature along the dimensions ‘measurement complexity’ and ‘weighted life-impact’. Based on this analysis, we have evaluated the different kinds of side effects according to the principles of biomedical ethics.

The most difficult ethical problem of STN DBS is posed by the fact that it may cause not only alterations of mood and intellectual capacities, but even personality changes (as understood in psychiatry). Each of the “Big Five” (i.e., the five basic personality traits: extraversion, neuroticism, agreeableness, conscientiousness, openness to experience; see Costa & McCrae 1992) has been influenced by STN DBS in some patients. We discuss whether STN DBS is generally unethical because of its potential to change the patients’ personalities. We answer in the negative, and argue instead for the necessity of evaluating the personality changes.

Finally, we formulate recommendations for future research and the clinical use of STN DBS. We demand that disclosure and informed consent before a DBS therapy should include specifications with regard to possible changes in personality and alterations of social behavior.

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5. Iatrogenic personality changes with the potential of harm for third persons: The dilemma of treating pedophilic Parkinsonian patients with deep brain stimulation

This chapter deals with a very special question that has been discussed on the brink of conferences about deep brain stimulation, both theoretically and with regard to an unpublished real case: What should a physician do if a Parkinsonian patient asks for DBS, and would be a perfect candidate from a medical point of view, but had been convicted of child sexual offense? If DBS would be only an effective treatment for a motor disability, physicians would not mind to treat a child molester, even if they might clandestinely think that it would be better for children if he would be sitting in a wheelchair. But since DBS experts know the possible psychiatric side effects of DBS, particularly the risk of hypersexuality, disinhibition and impulse control disorders, the prospect to treat such a patient induces fear: Does that mean "to jump the gun", as Elena Moro, editor of the European Journal of Neurology, has formulated it (Moro 2009)? And if such a patient would sexually (re-)offend, could the physician be not only accused morally, but also taken to court?

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6. Reviewing Autonomy. Implications of the neurosciences and the free will debate for the principle of respect for the patient's autonomy

This chapter analyses implications of the neurosciences and the free will debate for the bioethical principle of respect for the patient's autonomy. Henrik Walter and I suggest an elaboration of the concept of autonomy on the basis of neuroscientific knowledge and the free will debate. Since modern brain therapies have the potential to considerably influence the neural basis of autonomy itself, there is a desideratum for an elaborated, neuroscientifically funded concept of autonomy.

We argue that a sharp border between full autonomy and complete lack of autonomy does not exist, and that a large grey area between both exists, in particular in neuropsychiatry. Therefore, autonomy is not a categorical property but rather a gradual and changeable property of an individual. Not only does it increase from childhood to adulthood, but it may also decrease, e.g., due to brain damage or dementia. Furthermore, as autonomy is based on proper functioning of the brain, it can be influenced temporarily, as well as in the long run, by a multitude of factors, including disorders of the brain, but also by medication, recreational drugs, or physical interventions in the brain, e.g., deep brain stimulation.

If autonomy is a gradual and changeable property that depends on certain biological and social prerequisites, then respect for the patient's autonomy should not be a categorical issue but a gradual one, too. Therefore medical ethics needs a more elaborated concept of autonomy. We argue in how far such an elaboration can profit from the debate about free will and moral and legal responsibility between the philosophy of mind and the neurosciences.

After introducing this concept, we turn to two controversial examples in which a graded concept of autonomy is relevant: (1) the refusal to modify the parameters of deep brain stimulation when these parameters reduce the patient's self-control or cause manic, aggressive or deviant behavior, (2) the demand for the amputation of a healthy limb by persons suffering from Body Integrity Identity Disorder (BIID).

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Final Remark

In the meantime, Beauchamp and Childress have published the new edition of the "Principles of biomedical ethics" (7th edition, 2013). In this edition, they have stated their three-condition theory of autonomy more precisely; in fact, our criticism does not apply to the new edition anymore. Whether Beauchamp and Childress have reacted to our criticism or to that of other authors is unclear since they do cite neither our paper nor other papers. Nevertheless, in the current edition they define the third condition of autonomous action, namely "noncontrol", as follows: "that a person be free of controls either by external sources or by internal states that rob the person of self-directedness" (2013, p. 104). Although they concentrate on external controlling influences in the new edition, too, they declare: "but no less important to autonomy are internal influences on the person, such as those caused by mental illness" (2013, p. 105). Furthermore, they apply the statement that the condition of absence of controlling influence can be satisfied to a greater or lesser intent, to internal controlling influences, too. In fact, they state that "mental illness can be more or less controlling". Therefore they conclude that acts "can be autonomous by degrees, as a function of satisfying the two conditions of understanding and voluntariness to different degrees" and speak of "a continuum of both understanding and noncontrol". Furthermore, they justify that cutoff points on these continua are required, whereby "the lines between adequate and inadequate degrees of understanding and degrees of control must be determined in light of specific objectives of decision making". They state that "the appropriate criteria for substantial autonomy are best addressed in a particular context" (2013, p. 105).

Hence, the criticism of our 2010 paper has been taken into account implicitly and therefore it does not hit the seventh edition of the "Principles of biomedical ethics".

7. Discussion

In this final chapter I will scrutinize central issues of the former chapters: first the adequacy of Beauchamp and Childress' principle-based ethics for evaluating neurosurgical interventions which could alter the personality and/or the capability for autonomy (Chapter 7.1); second the concept of personal identity with regard to personality changes through brain interventions (Chapter 7.2); third the ethical evaluation of suchlike personality changes (Chapter 7.3). Fourth, I will derive general ethical recommendations for research and clinical praxis of neurosurgery with regard to its potential of altering the patients' personalities and capabilities for autonomy (Chapter 7.4).

7.1 Adequacy of the principle-based ethics for evaluating neurosurgical interventions which could change the personality or the capability for autonomy

Beauchamp and Childress' principle-based ethics, which has been published first in 1977 and developed further up to the seventh edition from 2013, certainly is the most influential position in medical ethics, particularly in the Anglo-American area. This ethical approach argues mostly on the level of so-called medium principles which are positioned between meta-ethical principles and detailed moral positions concerning special issues. The restriction to these more or less consensual medium principles (namely respect for the patient's autonomy, non-maleficence, beneficence, and justice) makes this approach very useful in both clinical praxis and medical research, since it helps to avoid fruitless debates on last principles. But although this strategy is a pragmatic way out, it is no general solution for fundamental ethical dissent, and its theoretical and practical adequacy as an ethical approach has been discussed broadly.

Beauchamp and Childress's ethics is exposed to critics from two sides: first from deductivists (e.g., Clouser & Gert 1990), second from the casuistic side (e.g., Jonsen 1995) (overview: Quante & Vieth 2002). Whereas the first criticize a lack of a universal, applicable ethical theory,[1] the latter criticize a too schematic application of principles to particular cases (Harris 2003)[2] and that it blocks substantive ethical inquiry (Callahan 2003). In a similar vein, the social science critique of bioethics claims that bioethics grounded in philosophy and moral theory gives a dominant role to idealized, rational thought and tends to exclude social and

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[1] Clouser & Gert (1990) have criticized that 'principlism' lacks systematic unity and consists of eclectic discussions emphasizing different types of ethical theory; since there is no moral theory that ties the principles together, there is no unified guide to action which generates clear, coherent, comprehensive and specific rules for action. Lustig (1992) has advocated the moral pluralism of Beauchamp and Childress as well as their skepticism about establishing any general lexical order among the principles. The difficulty of principlism to deal with conflicts among the principles has been addressed by several authors (e.g., Callahan 2003; Gardiner 2003; Harris 2003); it has not yet been solved sufficiently. Nevertheless, the ethical approaches of these commentators neither avoid ambiguity.

[2] Harris (2003) is convinced that following the four principles approach leads to "sterility" and "uniformity" and might let overlook possibly important features of a case.

cultural factors, so that it is isolated from practice (overview: Hedgecoe 2004). Critics come particularly from proponents of relational ethics (e.g., Sherwin 1998), communitarism (e.g., Callahan 2003), and virtue ethics (e.g., Campbell 2003; Charlesworth 2005; Gardiner 2003). The four principles approach has been criticized for its "neglect of emotional and personal factors", "coolness of the analysis", "oversimplification", "excessive claim to universality", or "imperialism" (Campbell 2003); it has been devalued as "a useful 'checklist'" for newcomers to bioethics (Harris 2003) and "at best pointless and at worst dangerous" being taught in medical schools (Cowley 2005). Particularly, the dominance of the principle of respect for autonomy has been criticised by many authors (critical overview: Gillon 2003). This criticism stems from different ideological backgrounds (Christian ethics, feminist ethics, care ethics, communitarism, or criticism of the Western culture). In spite of their diversity, they converge in giving collective benefits more weight than individual rights. Raanan Gillon (2003) has convincingly deduced why the principle of respect for autonomy should be regarded as *primus inter pares*, namely since it is an integral component of the other three principles.

Since I consider these fundamental criticisms of respect for autonomy as a potential threat for the acceptance of universal human rights and ethics in the tradition of enlightenment, I do not think that any of these approaches is a good alternative to the ethics of principles.

In favour of the four principles approach, Gillon (2003) has convincingly argued that it is rather a basis for moral ecumenism than an attempt at global moral imperialism. Furthermore, he has rightly shown that there is no necessary conflict between virtue ethics and the ethics of principles; both are required for a full moral theory, and they have a mutually dependent relationship. Although virtue ethics is valuable in medical education, it has significant limitations: First, virtue ethics needs some moral standard for being able to judge about character traits as virtuous or vicious. Second, with its focus on the character of agents, virtue ethics lacks the argumentative tools for dealing with difficult moral and legal dilemmas which lie beyond their good will. Third, virtue ethics in medicine supports medical paternalism by suggesting that all dilemmas could be solved if only the physician is virtuous.

Whether Beauchamp and Childress' ethics is adequate and sufficient for the ethical evaluation of interventions in the brain is discussed controversially, too. In favour of this approach speaks first that it allows for balancing benefits, risks and adverse effects of interventions in the brain; second its emphasis on the respect for the patient's autonomy and the procedure of informed consent. The latter is particularly important with regard to neurosurgery, since interventions in the brain bear significant risks of mental changes, whose valuation is an extremely individual issue that requires both good information of the patients and respect for their individual values.

Furthermore, the principle of justice is relevant for the ethical evaluation of neurosurgical interventions, since some ethical issues result from conflicts of interests. Patients' interests can be at odds with interests of their relatives, of providers of medical services, of producers of devices or drugs, or of research and education (Ford & Henderson 2006; Ford & Kubu 2006; Fins et al. 2011a). Especially in research domains which are characterized by an unavoidable mix of industry and academia, e.g., DBS research, there are multiple sources of conflict, including sources of funding, intellectual property exchange, and reimbursement specific to the conduct of research and practice (Fins et al. 2011a). Since many treatments of brain diseases are extremely expensive, they have to be justified in the rationing health care debate; therefore this context has to be considered in ethical investigations, too. On the one hand the request for maximum therapy could be driven by research or profit interests; on the other hand the claim for therapy limitations might be motivated by an interest in cost reduction. Beauchamp and Childress' approach is convenient to deal with these issues, too.

For these reasons, I have used Beauchamp and Childress' principle-based ethics for an ethical evaluation of the magnetic fluid hyperthermia therapy for malignant brain tumors (Chapter 2; Müller S 2009d), Markus Christen and me for DBS for Parkinsonian patients (Chapter 4; Müller & Christen 2011), Synofzik and Schläpfer (2008) for psychiatric DBS, and Henrik Walter and me for optogenetics-based DBS (Walter & Müller 2013). Also the guidelines for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic DBS (Fins et al. 2011a) are based on Beauchamp and Childress' principle-based ethics. Particularly with regard to possible personality changes caused by interventions in the brain, the application of the four-principle approach has been defended with the argument, that personality changes are neither good nor bad *qua change*, so "that there is no separate 'identity-based' ethical argument, distinct from the ordinary bioethical argument based on consent and well-being" (Baertschi et al. 2010; see also Synofzik & Schläpfer 2008).

Nevertheless, using this approach for neuroethical issues has some shortcomings and has been met with eligible criticism. For example, Samuel and Brosnan (2011) have criticized Müller & Christen (2011) for employing principlism as the bioethical model of evaluation of DBS. According to these commentators, Beauchamp and Childress' approach focuses narrowly on the patient as an individual. Samuel and Brosnan point to social influences on the decision-making of patients, particularly on the influence of the media which often hype new medical technologies. Since Parkinsonism and sometimes DBS threaten patients' relationships with others, they plead for applying a relational ethical framework, which understands relationships as constituting the individual self. Although their criticism is eligible, the maceration of the autonomy principle with regard to these patients is not justified, since most of them are autonomous persons and not subjects of the decisions of their relatives like coma patients or severely demented patients.

Kai Vogeley and Alfred Newen (2011) have developed a criteriology which is based on the ethics of principles, but exceeds it by taking into account first the central role of the brain for the person; second the brain's yet insufficiently understood complexity. Since interventions in the brain influence the experiencing and evaluating instance itself, an original neuroethical approach is required. According to Vogeley and Newen, the ethical evaluation of interventions in the brain should consider the following aspects: the *target* of the intervention, its underlying *model*, its *means*, its *goal*, and its *societal impact*. The *target* of an intervention in the brain is the functional domain whose neural mechanisms are influenced by the intervention. It has to be differentiated between perceptive, motor, affective and cognitive functions. Ethically relevant is particularly how close a function, which is to be influenced, is to the core of the personality. The *model* of an intervention describes the relevant available knowledge about the neural realization of the functional domain to be influenced. The ethical legitimation of a given intervention depends also on the empirical validity of the model. Ethical relevant aspects of the different *means* of interventions in the brain (ranging from psychotherapy over psychotropic drugs to neurosurgery) are the temporal patterns of the effects (since patients have better chances to integrate slow intervention-caused personality changes into their social and biographical contexts than immediate ones, which allows for more autonomous control of the changes), the reversibility, the adjustability and the duration of the effect of the intervention. Possible *goals* of interventions in the brain ─ namely therapy, prevention and enhancement ─ should also be differentiated from an ethical point of view. Particularly with regard to enhancement, Vogeley and Newen plead for balancing the autonomy of individuals and individual benefits with possible societal follow-up costs.

The criteriology of Vogeley and Newen is a helpful enhancement of the ethics of principles for the ethical evaluation of brain interventions, since it offers a sensible and practicable scheme for scrutinizing ethical issues which are specific for interventions in the brain.

In my view, with regard to interventions in the brain, the main challenge of the ethics of principles is raised by their potential to change a patient's personality and capability for autonomy ─ although such changes are not always problematic, but sometimes even desirable. In the following, I will discuss four arguments for this thesis.

a) Benefit and harm may be different pre- and postoperatively

Since some interventions in the brain can change fundamental properties of the person, including her personality (in terms of psychiatry), her main interests, her purpose in life and her personal value system, what counts as benefit or harm for her, can be changed, too. By way of example, for a Parkinsonian patient, whose purpose in life is his profession, benefit and harm of DBS are defined in terms of capability for work. If the formerly conscientious, hard-working patient becomes hedonistic under DBS, so that his purpose in life shifts from work to leisure activities, then benefit and harm will be defined postoperatively in terms of capabilities for these activities. Thus, pre-operatively, a possible deterioration of verbal memory would have been a fatal harm for the patient, but after DBS, it would not bother him, since it would not disturb his leisure activities. The other way round, preoperatively, the patient would have seen a great benefit in becoming even more conscientious; after DBS he prefers to be less conscientious, since consciousness could reduce his ability to have fun.[3] Particularly for Parkinsonian patients, it has been observed that their goals and expectations for DBS evolve over time in a dynamic manner such that some goals and symptoms become more paramount over time while others lessen in importance (Kubu & Ford 2012).

Thus, for interventions which could change the personality of patients significantly, the application of the principles beneficence and non-maleficence is not impossible, but can be very difficult, since the evaluation of beneficence and non-maleficence may differ significantly pre- and postoperatively. Therefore, a benefit-harm-analysis of interventions in the brain should comprise benefit and harm from both the pre- and the expectable postoperative perspective. This proposed strategy does not question Beauchamp and Childress' approach but suggests how its application should be elaborated further with regard to interventions which might affect the patient's personality and personal value system.

According to scholars, who think that the personal identity of patients is threatened by DBS or other interventions in the brain which alter the personality significantly, the principle of beneficence cannot be applied at all, since the patient is turned into a different person. By way of example, Glannon (2009) asks: “So even when a medical procedure is effective, can it be justified if it radically alters one's life narrative and effectively turns one into a different person?“ And he concludes: “One might question how an individual could benefit from a treatment if his or her identity changes as a result of it. If the alteration of mental states is substantial, then it is unclear who the beneficiary of the treatment would be. The individual experiencing the positive effects of the treatment would appear to be a different person from the one who requested the treatment.” In Chapter 7.2, I will argue against the idea that the personal identity is changed by interventions in the brain. This idea would indeed question the

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[3] Schüpbach et al. (2006) have reported such changes of purposes in life: “Sixteen patients had a professional activity before surgery. Five patients no longer wanted to work after surgery, giving priority to leisure activities: ‘Before, I thought that work was the most important thing in my life. Now, I want to do other things. I realize that my presence at work is not essential, and that the work gets done even when I'm not there.’” Whether these changes are caused mainly biologically or by the experiences of disease and therapy, is an open question.

application of the ethics of principles on interventions in the brain much more fundamentally than my argumentation.

b) Challenge to the principle of respect for the patient's autonomy

The greatest challenge is posed to the principle of respect for autonomy since interventions in the brain can change the capability for autonomy fundamentally. When a patient has to decide about an intervention in his brain, the very subject of autonomous decision-making has to decide about his future capability for autonomy which might be destroyed, deteriorated, restored, enhanced or not be affected, respectively, by the intervention in the biological basis of his autonomy.

However, respect for autonomy is central for patients who have to decide about an intervention in their brains at least as much as for other patients.[4] Therefore I do not plead for limiting or questioning this principle; rather I plead for further elaborating and refining it with regard to interventions which might affect the patient's capability for autonomy.

First, it should be taken into account that a patient's autonomy is not a categorical property which is either substantially lacking or existing, but a gradual property (Chapter 6; Müller & Walter 2010; Walter 2001). This issue has been acknowledged by Beauchamp and Childress in the most recent edition of their work (7th edition, 2013, p. 105). Now, the task is to elaborate this insight, particularly with regard to patients with brain diseases and mental disorders. Second, autonomy is a multi-facet property which is best described in several dimensions. Third, the capability for autonomy depends on several cognitive, executive and affective functions that have certain biological and social prerequisites which have to be developed and which can be compromised to different degrees. Therefore, Henrik Walter has proposed a neuroscientifically funded concept of autonomy which is based on the three dimensions alternativism, intelligibility, and authorship (Walter 2001). Important for a comprehensive understanding of autonomy is that it is not only based on cognitive abilities and deliberation, but also on the ability of self-control, an intact (emotional) evaluation system and power of judgment. This is of particular importance for evaluating the autonomy of persons whose cognitive abilities are intact, but who show characteristic emotional deficits, lack of self-control, or impulse control disorders. Examples are brain-injured patients with acquired psychopathy (pseudopsychopathy, Phineas Gage-type) for whom it is unclear in how far they have the capability of autonomy (Christen & Regard 2012).

With regard to changes of a patient's capability for autonomy through brain interventions, three cases have to be differentiated: Interventions can (1) destroy or deteriorate the capability

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[4] An interview study with neurosurgery patients showed that nearly all placed emphasis on patient autonomy and informed consent, also with regard to interventions which entail significant risk to mind or body (Lipsman et al. 2009; n = 27).

for autonomy, (2) restore or enhance it when it is disturbed by disease or trauma, or (3) allow the patient for manipulating it. The following examples illustrate the three different cases.

1. Case: Destruction or deterioration of the patient's capability for autonomy

Example: An autonomous patient suffering from an aneurysm decides for a neurosurgical intervention. Since he is convinced that he would rather wish to die than to live without his intellectual abilities and his capability for autonomy, he demands in his advance directive to let him die, if these capabilities would be annihilated by an irreversible brain damage. Unfortunately, an intra-operative bleeding destroys large areas of his brain irreversibly, so that he awakes from surgery without his autobiographic memory and with no more cognitive abilities than an infant. Additionally, he depends on life-saving support. The formerly autonomous subject that had decided about an intervention in his brain has changed postoperatively into a person who is incapable of autonomous decision-making and does not remember his pre-operative decisions. The pre-operative subject would not have recognized himself in his post-operative form of existence; nevertheless, he does not seem to suffer. Following Beauchamp and Childress, the previously expressed autonomous wishes of the now-nonautonomous person have to be respected (2013, p. 229); therefore the patient should be allowed to die.

Several authors have questioned whether the post-operative person is really identical with the pre-operative person by referring to a psychological continuity theory of personal identity. According to these theories, persons are defined by certain psychological criteria; thus a person ceases to exist after an event which disrupts her psychological continuity and is then replaced by either a new person or a non-person. This theory has been discussed with regard to advance directives: If a person ceases to exist when her psychological continuity is disrupted by a given event, then any advance directive written before that event would be invalid for the person after this event, since the former person had no right to decide about the future of the new person – just because the latter is a distinct person or a "non-person" (Buford 2008).

If legislation would follow this argumentation, the aneurysm patient would not have any possibility of deciding autonomously in advance for a possible later state of missing autonomy. As I will scrutinize in Chapter 7.2, the principle of respect for autonomy is indeed challenged by suchlike cases, but argumentations based on the psychological continuity theory of personal identity are misleading: Finally they sacrifice the respect for autonomy instead of refining the concept of autonomy so that dilemmas posed by iatrogenic deteriorations of the capability for autonomy could be analyzed comprehensively.

2. Case: Restoration or enhancement of the capability for autonomy

Example: A pregnant single woman loses rapidly her ability to communicate verbally, and her consciousness fades temporarily. A MRI scan reveals a large edema and several brain metastases, probably originating from breast cancer which had been treated several years ago. A cortisone therapy fails to shrink the edema sufficiently; thus the patient's consciousness remains severely disturbed. The physicians discuss whether the brain metastases should be treated aggressively with neurosurgery, radiosurgery, and chemotherapy in order to prolong her life and improve her remaining quality of life. But these interventions would harm the five months old fetus severely and possibly kill it. For the fetus' sake, several treatments, particularly chemotherapy, should be delayed until delivery, but then the woman's life-span would be significantly reduced. Since the woman is momentarily not able to understand the treatment options she can neither consent to any intervention nor refuse them. Of course, a custodian could substitute her will and decide about life and death of mother and child, possibly without knowing anything about her values and preferences. But the dilemma could be solved by the physicians, the custodian and the responsible judge in a way that respects her autonomy, namely by restoring her capability for autonomy and thus enabling her to decide autonomously. Concretely, they should decide for a neurosurgical treatment of the edema and the tumors which are momentarily affecting her consciousness and understanding. This intervention is possible with minimal risks for the fetus. If this operation is successful, the woman's capability for autonomy will be restore, so that she can decide autonomously about her further treatment, particularly about giving priority to her own or the fetus' life.

Respect for the patient's autonomy is understood in bioethics mainly in terms of respecting the patient's free decision about treatment after being informed about its benefits, risks, and alternatives and after understanding its consequences. With regard to brain diseases and interventions in the brain, an additional aspect should be emphasized, namely the goal of saving or restoring the patient's capability for autonomy. As I have argued in Chapter 2, respect for the patients' autonomy is realized first of all by saving the brain functions underlying the capability for autonomy, if they are threatened by a brain disease or trauma. Respect for autonomy does not mean only to respect existing autonomy, but beyond that, to engage in saving or restoring the biological and social prerequisites of autonomy if they are endangered.

Both the principle-based approach and its critical commentators have mainly considered social influences which can threaten autonomy. Not until the seventh edition from 2013, Beauchamp and Childress have defined the third condition of autonomous action, namely "noncontrol", as being "free of controls either by external sources or by internal states that rob the person of self-directedness" (p. 104). Nevertheless, also in the most recent edition, Beauchamp and Childress concentrate on external controlling influences. But "internal influences on the person" are most important with regard to brain diseases, brain traumata, mental disorders, and intervention-related brain lesions. Beside malignant brain tumors, severe neurological and mental disorders such as dementia, schizophrenia and addiction threaten the autonomy of patients.

In a widely-used narrow understanding of the principle of respect for autonomy, it is reduced to the negative obligation, namely that autonomous actions must not be subjected to controlling constraints of others. But, as Beauchamp and Childress have clarified, this principle can be stated as both a negative and a positive obligation: As a positive obligation, the principle of respect for autonomy requires also "actions that foster autonomous decision making" (2013, p. 107). Although Beauchamp and Childress explicate this requirement in terms of disclosing information, probing for and ensuring understanding and voluntariness, and, where required, helping patients make decisions, I plead for understanding the positive obligation more comprehensively, namely so that actions that foster autonomous decision making comprise also actions which save, support or restore the patient's capability of autonomous decision making if it is challenged, for example by brain disorders.

This understanding is necessary especially from a neuroethical perspective since particularly disorders of the brain threaten the capability for autonomy. It corresponds with my former argument that not only interventions in the brain, but also their waiving can be ethically problematic (Chapter 1.2; Müller S 2009 d). Furthermore, it is the philosophical basis for the justification of compulsory treatments of patients with severe mental disorders, e.g., psychosis, in order to restore their capability for autonomy (Müller S et al. 2012 a+b). In a similar vein, Arthur Caplan (2008) pleads for temporary mandatory treatment of addicts (with drugs such as naltrexone) in order to relieve "the coercive effects of addiction and permits the recreation or re-emergence of true autonomy".

3. Case: Possibility for patients to manipulate their own capability for autonomy

Example: A Parkinsonian patient, who is treated with STN DBS, receives a remote control with limited functionality which allows him the modification of the stimulation parameters within a certain range in order to optimize his motor functions. An individual adaptation of parameters is necessary for the patient, because no parameter set is optimal for all activities of daily life: With the parameter set, which is optimal for walking, his articulation is poor; with another parameter set, his articulation is better, but his walking is worse. The patient discovers that the different parameter sets do not only influence his motor functions differently, but also his mood, behavior and certain personality properties. After a period of systematic experimentation with the parameters, he finds out which parameters he has to set in order to become either fun-loving or rationalistic and conscientious. He knows (also from discussions with his wife) that in his fun-loving state, he is able to get enthusiastic, uncritical and even hypomanic, whereas in his rationalistic and conscientious state he tends to be overcritical and unsmiling.

When he considers these observations (during his rationalistic state), he decides to optimize his parameters always so that he will function optimally in the expectable social situation: Before a counseling interview in his bank he will make himself rational and conscientious; before joining a party he will allow himself his fun-loving state. Unfortunately, this strategy does not work for long: After a party, which he enjoyed very much, he decides not to switch his parameters back to the rational state, because he does not want to become unsmiling and overly serious again. In the following weeks, his happiness becomes hypomanic, and he starts making hazardous financial transactions for the first time in his life. His wife cannot convince him to reduce the stimulation; she is concerned about his behaviour and doubts whether he still is contractually capable. Finally, the Court of Protection makes her his deputy.

Seemingly, some DBS patients, who possess a remote control for modifying the stimulation parameters within a certain range, can optimize themselves for different demands or needs ─ not only their motor functions, but also their emotional state and thus their behavioral dispositions. After all, some patients can literally modify their own capability for autonomy.

At the first glance, the situation resembles the situation of alcohol consumers, who also can influence their own capability for autonomy by choosing to drink or not to drink a certain amount of alcohol. But there is an important difference: For some patients with STN DBS, the very parameter set which optimizes their motor functions can cause hypomania and thus threaten their capability for autonomy; for alcohol consumers it is just the other way round. The problem of STN DBS with regard to autonomy is that some patients are tempted to decide autonomously for reducing their own capability for autonomy, not because they want to lose their autonomy, but because they want to optimize their motor function and/or mood. Thus the loss of autonomy is an adverse effect of an otherwise sensible decision, not of an autonomous decision to lose autonomy. In the first step, the decision may be autonomous and even rational: For the patient described in the example, it is sensible to select stimulation parameters which optimize his motor functions and mood always in accordance with expectable social situations. The problem is that the way back could be closed, if once a hypomanic state has developed.[5]

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[5] This problem has been discussed by Glannon (2009) with regard to the case described by Leentjens et al. (2004): “[The patient] autonomously and knowingly chooses an option that immediately makes him mentally incompetent and devoid of decisional capacity. […] While the patient’s decision has the effect of binding him to state of mental incompetence, it is not his intention in opting for stimulation. The mania is an undesirable but acceptable side effect of the realisation of his intention to relieve the suffering he experiences in his loss of motor control. Yet his decision would have the effect of precluding any possibility of changing his mind. Paradoxically, an autonomous decision to consent to a medical treatment would make him lose his autonomy and capacity to subsequently choose to continue this treatment and to have or forego others.” (p. 291). Glannon argues that the physicians should offer the patient to revisit the question of whether to continue or discontinue DBS at a later time. For that, the stimulation should be stopped so that the mental competence could be restored and the patient and the physicians could discuss treatment options.

The patient's goal is to influence his own mood according to his rational mood-managing strategy, i.e., to be always in the mental state that is optimal for his long-term life-planning. He considers his rational mood-managing strategy to be stable ─ but that is not the case. Rather, by adapting the stimulation parameters in order to be in the appropriate mood (e.g., to be fun-loving when going to a party), he influences himself so that his mood-managing strategy is modified, too: After a while in the fun-loving state, he does not want to become conscientious again, and therefore his mood-managing strategy changes, too: Now he wants to be always in the mood which makes him most happy; he nearly cares for his former long-term life-planning. Thus, his behavior changes; e.g., he makes hazardous instead of conscious financial transactions; he spends a lot of money for having fun instead of saving money for his long-term goals.

The situation is paradoxical: DBS enhances the patient's autonomy on the first level (for he can decide about his own mental state including his capability for autonomy), but makes him lose his autonomy on the second level since his higher-order strategy is replaced by less rational, more short-sighted and emotional strategies stemming from the stimulation-induced mood. Consequently, he cannot find the way back from the hedonistic, hypomanic and less autonomous state to a normal level of mood and capability for autonomy, so that finally, his autonomy is significantly reduced in the three dimensions alternativism, intelligibility, and authorship. In such cases, the additional autonomy goes into reverse.

Furthermore, some patients seem to be able to influence the degree of their own ability for socio-moral judgment, as an experiment of Bothe and colleagues suggests: Two out of 15 patients were socially maladjusted after STN DBS for more than one year. When the stimulation was switched on in these two patients, their power of socio-moral judgment (measured with the 6-level Kohlberg scale; Kohlberg 1984) decreased from level 4 (adhering to social system and conscience) to level 2 (serving one's own interests and letting others do the same). This effect was reversible when the stimulation was switched off, i.e., the power of socio-moral judgment normalized again (Bothe 2003; Brentrup et al. 2004). This allows the conclusion that the moral competence of some DBS patients can be literally switched on and off – possibly even from the patients themselves.

Some patients might even seek to change personality traits "for frivolous reasons" (DeGrazia 2005b, p. 279), e.g., someone could try to make himself more reckless and more aggressive in order to have more fun and success in martial arts.

If respect for autonomy is restricted to the negative obligation, then physicians would have to accept cases of autonomy loss as a consequence of autonomous decisions. But if respect for autonomy is understood also as a positive obligation, then physicians should save patients from a loss of their autonomy as an adverse effect of medical treatment. Therefore, by limiting the patient's decisional scope about his own stimulation parameters, the patient's autonomy could be saved against a stimulation-induced deterioration of his capability for autonomy. On the other hand, if physicians limit the stimulation range, the patient's mood and personality is partly controlled by the physicians. Of course this is necessary for clinical reasons, but beyond that, a (moral) valuation of the mental state of the patients will also play a certain role. From the patients' subjective perspective, this might be experienced as a limitation of autonomy or even as being manipulated by the physicians.[6] Furthermore, the patient's family or carers may want some say in choices over treatment outcome; they might prefer personality traits more like the familiar traits before DBS, whereas patients are likely to choose stimulation parameters enabling them to feel better than well. Therefore, some conflicts of interest may arise between clinicians, patients, and family (Mackenzie 2011). Family and carers may also experience the patient as being less autonomous, especially if they discuss with the physicians about the stimulation parameters and their effects on the patient's personality and behavior ― thus making the patient's personality an object of common decision-making. If they witness the nearly immediate changes the patient undergoes under different stimulation parameters, they might doubtfully ask under which parameters the patient is really himself, i.e., authentic.[7] Just the rapidness of the effects of DBS on mood and behavior, makes it difficult to integrate them into the person's self-image; thus the person could develop feelings, emotions, and moods which are not authentic.[8] Inauthenticity occurs particularly if stimulation-induced feelings cannot be integrated into the self-image and value system of the patient. For example, a conservative Christian man, who became hypersexual under DBS for OCD, suffered from severe suicidal ideation due to DBS-induced hypersexuality and persistent symptoms. Apparently, he experienced a severe conflict between his emotions and his value system and self-image.[9] On the other side, some patients feel like awaking or finding their true selves after DBS; they experience their mental state following DBS as authentic, even when their caregivers and psychologists describe it as maladaptation (Kraemer 2013).

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[6] Hildt (2006) describes this phenomenon as follows: "This may lead to the impression of being ― in one's essence ― manipulated by the electrode system." ― Indeed, some patients utter the feeling of being controlled by the device ("I'm an electronic doll"; "I feel like a 'Robocop'"; "I'm under remote control") (Agid et al. 2006).

[7] For a discussion of the authenticity of mood and emotions under DBS, see Leefman et al. (2011). The authors discuss the close linking of autonomy and authenticity. They define authenticity as the autonomous pursuit of a coherent self-image that integrates social, cognitive and emotional properties of the person. The authenticity of a personality should be considered as a normative ideal; since personalities are dynamic, authenticity has to be always developed anew.

[8] Leefman et al. (2011) argue that just the rapidness of the effect onset is ethically relevant. In contrast, pharmacotherapy and even more psychotherapy need several weeks for being fully effective; thus patients are more able to integrate their effects into their self-image.

[9] Case study: Chang et al. (2010); discussion of the case: Leefman et al. (2011).

The problem of autonomy loss is even aggravated for patients treated with DBS of the reward system. Some patients who were treated with DBS of the septal area for intractable pain and who possessed a remote control for adapting the stimulation, became addicted to the stimulation itself.[10] The reason for that is the phenomenon of brain stimulation reward which was first observed in rats that were allowed to stimulate their own reward system by pressing a lever; some rats continued to stimulate until they exhausted themselves. With such a self-stimulating procedure, the brain stimulation reward may become uncontrollable for humans, too (Oshima & Katayama 2010). DBS of the reward system may be an effective treatment of not only major depression and obsessive-compulsive disorder, but also of obesity and addictions (Halpern et al. 2011). If physicians allowed patients to perform self-stimulation, it can be expected that the patients become addicted to stimulation. On the other side, if physicians prevent self-stimulation and employ the stimulation just to adjust the patient's mood and reward-behavior within the normal range, then the patient's mood is controlled by the physicians (Oshima & Katayama 2010). Since DBS of the nucleus accumbens can directly induce elevated mood, and even hypomania, whose degree can be specifically modulated by changing the stimulation parameters (De Koning et al. 2011; Goodman et al. 2012; Synofzik et al. 2012), someone will have to determine the optimal level of mood. Patients might demand higher than "therapeutic levels of happiness". Suchlike conflicts point to the limits of patient's autonomy (Synofzik et al. 2012). Legally, physicians are not obliged to fulfill a patient's demand for stimulation settings which would increase the mood beyond established therapeutic levels, particularly if these settings might involve additional risks.[11]

Nevertheless, difficult neuroethical questions remain: Who has the right to determine and control the mental condition of a patient? Who decides about the therapeutic range, not only of parameter settings, but also of the mental outcome, particularly of the level of mood? How much stimulation-induced happiness is good for the patient and for his surrounding? How can the patient's autonomy be protected best between the Scylla of physician-control over his mental state and the Charybdis of addiction? These questions cannot be answered by just referring to medically established values since they conceal underlying moral values, e.g., an understanding of a good degree of happiness. Rather they require a reflection of issues of

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[10] Overview: Oshima & Katayama 2010. — A few additional cases of addictive self-stimulation have been reported from different DBS targets and different indications: Portenoy et al. (1986) describe a woman with chronic pain treated with DBS of the right thalamic nucleus ventralis posterolateralis who developed compulsive self-stimulation associated with erotic sensations and changes in autonomic and neurologic function. Schmidt et al. (1981) report a patient with postamputation pain, whose mediothalamic system was stimulated, who developed a behavior similar to addiction. Morgan et al. (2006) report a Parkinsonian patient treated with STN DBS who experienced a "morphine-like feeling" by self-stimulation.

[11] Goodman & Alterman (2010) say with regard to psychiatric DBS that "it would be problematic if the patient could self-induce hypomania".

good life, good personality, and good mental states. For these issues, the four-principle approach obviously is not sufficient.

c) Changes in personality which might be harmful for third persons

An important shortcoming of Beauchamp and Childress' biomedical ethics is that it solely refers to the rights and interests of the patient, neglecting the rights and welfare of third persons who might be indirectly affected by the patient's treatment, particularly by iatrogenic changes of the patient's behavior. The four principles suffice only to ban interventions which could harm the patients themselves or disregard their autonomy, but fail in banning interventions which will exclusively harm third persons, particularly as a consequence of therapy-induced changes in personality and behavior. Paradigms are interventions which cause or strengthen a person's disposition for immoral or even criminal behavior, for example by reducing his capabilities for empathy, moral judgment, impulse control or self-reflection; diminishing his respect for social or moral norms; or inducing hypersexuality, aggressiveness or recklessness. Although presumably most persons would object to interventions which might turn them into psychopaths or sexual offenders, some persons might welcome interventions which could increase aggressiveness or reduce (sexual) inhibition. This shortcoming has been elaborated for the paradigmatic case of pedophilic Parkinsonian patients demanding for DBS, whereby the risk of offending children could be increased (Chapter 5).

Dilemmas resulting from therapies, which are beneficial for the patient but potentially harmful for other persons, reveal conceptual limits of Beauchamp and Childress' ethics. This shortcoming could be healed by expanding the application of either the principle of nonmaleficence to third persons, who are indirectly concerned by a given therapy, or by elaborating the principle of justice so that such conflicts of interest can be solved. But Beauchamp and Childress have not explicated these principles in this way. Instead, they have straightened out that the patient's autonomy has only a prima facie standing and that a patient's decisions which potentially harm others might be overridden by competing moral considerations (2013, pp. 107-108). A drastic example is a patient with renal failure who autonomously decides for receiving the kidney of a healthy person who does not want to donate or sell one of her kidneys. This acknowledgment refers to the conceptual limits of their ethical approach. But beyond this necessary limitation of patient's autonomy with regard to the rights of third persons, iatrogenic changes in personality and behavior which threaten the rights of third persons raise a new and specifically neuroethical issue: Do benefits for patients justify the risk that their personalities are changed so that they become more dangerous for third persons than they used to be?

d) Ethical evaluation of changes in personality

Finally, the ethically decisive question is not *whether* interventions in the brain can alter the personality or not, but whether they do so *in a good or bad manner*; i.e., first whether the *result of change* is good or bad; second whether the *way of change* is good or bad. The valuation of iatrogenic changes in personality is a normative, not an empirical issue. It requires criteria both for good personality properties and for good ways of changing personality properties. These criteria cannot be derived from the approach of Beauchamp and Childress, just because it is restricted to the medium principles. Certainly, consensus exists neither with regard to good personality properties nor to good ways of modifying them; attitudes about both aspects depend strongly on culture and ideology. Nevertheless, a minimal consensus is not utopian and could be elaborated by a modern, universalistic virtue ethics. However, psychiatry cannot avoid evaluating personality properties, because it aims at changing certain negatively evaluated properties (Müller & Christen 2011). But insofar psychiatry is an empirical science it cannot found values, but only refer to values taken from society, from moral theory and/or virtue ethics. This issue will be scrutinized in Chapter 7.3.

Conclusion

Summarizing, it can be stated that personality changes caused by interventions in the brain require ethical considerations which transcend Beauchamp and Childress' approach, although it is *prima facie* adequate for evaluating the risk-benefit-ratio for patients, respecting the patients' autonomy and considering issues of justice. Nevertheless, at least the standard interpretation of the principles is too narrow to deal with the specific ethical issues in the context of interventions in the brain. First, principle-based risk-benefit assessments require a broader perspective that includes all foreseeable consequences of the treatment for the patients and for third persons, particularly consequences which might result from therapy-induced personality changes. Second, the concept of autonomy has to be elaborated whereby the dependency of the capability for autonomy on brain functions has to play a central role, namely with regard to the positive obligation to save, restore or enhance this capability if necessary. Third, for the ethical evaluation of therapies with might cause personality changes, an ethical valuation of personality changes is required, since neither the conservative general condemnation of technically caused personality changes nor a libertarian abstinence in valuating personality is helpful for medical ethics. Whereas the first issue could be integrated into the ethics of principles; the third issue clearly outreaches any ethics on the level of medium principles.

Since brain interventions raise a number of both specific and fundamental ethical questions, particularly with regard to their potential of changing the personality, a genuine neuroethics is required.[12]

7.2 Are the concepts "loss of personal identity" or "replacement of a person" appropriate to describe personality changes after brain interventions?

A main concern with regard to interventions in the brain is that the patient's personality might be significantly changed: "The fear is often expressed that an individual may no longer be 'the same person' he or she used to be prior to an intervention in the brain. In other words (i.e. philosophical terms), these interventions are said to threaten personal identity." (Merkel et al. 2007, p. 4). Several scholars question whether the post-operative person is really identical with the pre-operative person by referring to psychological continuity theories of personal identity. Some authors refer to Parfit, who claims that a person ceases to exist after an event which disrupts her psychological continuity and/or connectedness and is then replaced by a new person. Parfit's theory has been transferred from philosophy of mind to real-life issues; particularly it has been used in discussions about advance directives (Buchanan 1988; Buford 2008), especially about Ulysses contracts[13] (critically: Quante 1999). In the last years, ideas about the loss or change of personal identity have been transferred to ethical discussions about DBS (Brand 2009; Glannon 2009; Klaming & Haselager 2013; Mackenzie 2011; Merkel et al. 2007; Müller O et al. 2010; Northoff 1996, 2001 and 2004; Stier 2006; Witt K 2013; Witt K et al. 2012 and 2013), intracerebral stem cell transplantations (Goldstein 2011), and treatments of malignant brain tumors (Anderson-Shaw et al. 2010).

Indeed, personality changes occur in a significant fraction of patients who undergo neurosurgery. In extreme cases, patients utter that they feel as different persons. The problem of personality changes after brain interventions has been underestimated for a long time; not since a few years has it come to the focus of bioethics. Particularly personality changes following DBS are intensively discussed by ethicists, whereby personality changes caused by other neurosurgical interventions, e.g., epilepsy surgery, still do not receive much ethical attention. But from the clinical and ethical relevance of this issue cannot be deduced that its conceptualization with the help of psychological continuity theories of personal identity is

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[12] For the role and scope of neuroethics see e.g. Alpert 2008; Farah 2002, 2005 and 2012; Fischbach & Mindes 2011; Illes (ed.) 2006; Levy 2008; Racine 2010; Roskies 2002 and 2010.

[13] "Ulysses contracts" are psychiatric advance directives. They allow mentally ill persons who are competent and with their disease in remission, and who want timely intervention in case of future mental crisis, to give prior authorization to treatment at a later time when they are incompetent, have become non-compliant, and are refusing care. Ulysses contracts raise a number of ethical issues: of their moral authority, of personal identity, of the status of possible revocations of the advance directive during a crisis, and of the risk of misuse and abuse (Widdershoven & Berghmans 2001).

adequate, be it from an ethical or a neurophilosophical perspective. In this section, I will argue why metaphysical ideas of "loss of the personal identity" or "replacement of the person" are inappropriate and misleading for ethical analyses of the issue of personality changes caused by brain diseases or brain interventions.

Clinical examples of "becoming a different person"

A few examples may suffice to illustrate the spectrum of persons who seem to have become different persons after brain traumas, brain diseases, or brain interventions, respectively.

1. Personality change after brain trauma: The famous historical case of Phineas Gage is the paradigmatic case of a frontal lobe syndrome caused by a traumatic brain lesion (Harlow 1868). Well-known is the statement passed down by one of his colleagues: "Gage was no longer Gage".

2. Change in sexual orientation after stroke: A 57-year-old homosexual man became heterosexual after a second dominant hemisphere infarct. His homosexuality had been accepted by the patient, his social network and family members. Six months after the second stroke, the patient started complaining of his changed personality and heterosexual orientation. Additionally, he reported excessive mood swings and changed interests, particularly a preoccupation with photography. His sexual orientation remained heterosexual at least 4 years following the second stroke (Jawad 2009).

3. Serial murder after brain trauma: The so-called Monster of Terrazzo was accused of several murders. At the age of 16, Gian Stevanin had been in an accident after that he had gone into a coma for several months. Thereafter his personality had changed dramatically: The formerly friendly young man had become addicted to pornography and committed many crimes of all sorts; finally he tortured, raped and killed several prostitutes in an extremely sadistic manner. Although his lawyers presented MRI scans which showed an orange-sized atrophy of his forebrain, the court did not exculpate him for insanity.[14] The idea suggests itself: Is the "Monster of Terrazzo" really the same person as Stevanin was before the accident?

4. Subjective experiences of personality change after tumor resections, epilepsy surgery or neurosurgery for mental disorders: Some patients with surgical lesions in the "affective division" of the anterior cingulate cortex reported "very marked emotional changes" and "such profound effects on daily life that they felt that they had in some ways become different people since their surgery" (Hornak et al. 2003). After temporal lobe surgery for epilepsy, some patients reported that they "feel like a different person", especially with regard to a greater sense of self-confidence and independence, in some cases leading to separation from the part-

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[14] The judges argued that he had sufficient insight to understand the wrongness of his deeds; therefore he received a life sentence (Gainotti 2001; Markowitsch & Siefer 2007: 116-123).

ner, a new self-image and lifestyle and a change in sexual orientation (Baird et al. 2002). After capsulotomy for OCD, major changes in personality are observed in some patients, of whom some are very satisfied with the outcome; whereby sometimes their view conflicted with their relatives' view. For example, one disinhibited patient concluded that she had "finally found her true personality" (Rück et al. 2008).

5. Personality and behavioral changes after DBS: After DBS, some patients experience significant changes in personality or have "the feeling that identity has been affected" (Gisquet 2008; Schüpbach et al. 2006). Family members sometimes report that the patient is not like he was before DBS (Gisquet 2008; Müller O et al. 2010; Tammer 2006), whereby in some cases the patients seem to become under DBS more the persons they were before psychiatric symptoms emerged (e.g., Gabriëls et al. 2003, case 2; Schüpbach et al. 2006). But some patients who were successfully treated with DBS had problematic changes in personality and behavior; e.g., some developed hypomania and hypersexuality (Chang et al. 2010; Doshi & Bhargava 2008; Houeto et al. 2002; Krause et al. 2001; Roane et al. 2002; Romito et al. 2002), violent behavior and kleptomania (Sensi et al. 2004), reckless car driving (Romito et al. 2002), compulsive buying (Leentjens et al. 2004; Romito et al. 2002; Herzog et al. 2003), or exhibitionism and leisure tourism (Houeto et al. 2002).

Suchlike clinical findings are paraphrased as "loss of the personal identity" (Merkel et al. 2007, p. 4), "substantial change in his identity" (Glannon 2009), "becoming another person" (Witt K et al. 2013), "instantaneous apparent identity changes" (Mackenzie 2011) or (less dramatically expressed) "(at least certain aspects of) personal identity [are] affected" (Jotterand & Giordano 2011). With regard to the patients' significant others, Robin Mackenzie (2011) thinks that "patients may not behave or feel like familiar damaged or diseased loved ones, but healthy strangers with claims on family/carers' time, affection, and assets". Karsten Witt et al. (2013) state: "The risk of becoming another person following surgery is alarming for patients, caregivers and clinicians alike."

Are these statements justified or exaggerated? To answer this question, a closer look at the philosophical concepts of "person", "personhood", and "personal identity" is necessary.

Person and personhood

The bioethical discussion about changes in personal identity and the loss of personhood is grounded on the philosophical concept of a person, whose core ideas have been developed by John Locke (1690). Locke has defined a person as "a thinking, intelligent being, that has reason and reflection, and can consider itself as itself, the same thinking thing in different times and places" (ibid., II.XXVII, § 9, p. 208). He distinguishes persons from human beings; whereas the identity of a human being is founded in its living body, the identity of a person is constituted by its (self-) consciousness. For Locke, "person" is basically a "forensic term appropriating actions and their merit" (ibid., II.XXVIII, § 26, p. 218): A person is a being that can be held responsible for its actions. According to Dirk Hartmann and Thorsten Galert's elaborate analysis of the concept of a person (Merkel et al. 2007, pp. 189-287),[15] a person needs to have a concept of itself; "which in turn demands cognitive capacities to such an extent that it can be said to be a subject of experiential knowledge, a participant in a community of language users, and as such locatable within the common objective world the community intersubjectively constitutes" (ibid., p. 218). This definition comes very close to Locke's straightforward definition of a person. According to Hartmann and Galert, being a person, means to be a *moral agent*, i.e., a (potential) subject of duties. The concept of agency presupposes a certain kind of freedom of the will, i.e., persons need to be able to exercise a certain degree of control over their actions (ibid., p. 230).

Personhood, as understood by most modern philosophers in Locke's tradition, cannot be prescribed to all human beings, particularly not to babies and humans in persistent coma. There can be persons that are not humans and humans that are not persons. Consequently, human beings who are no persons do not have the rights that are based on the status of a person. Several Utilitarian bioethicists (e.g., Peter Singer) support this position; they refuse human "non-persons" rights which are based on personhood, whereas they demand them for nonhuman animals that fulfill the criteria of personhood. This strict position has been softened by Hartmann and Galert, who argue that human beings, who are no persons, nevertheless have rights; they are *moral objects*, although they are no *moral subjects*; i.e., they do not have any duties and cannot be held responsible (ibid., pp. 213 and 224).

Vogeley and Newen (2011) emphasize that it is necessary to differentiate between a normative and a theoretical-empirical idea of personhood. They state that the normative idea of personhood is intrinsically tied to the idea of human dignity; and that its main task is to define boundaries for ethical consideration in order to include or exclude, respectively, certain categories of beings (e.g., nonhuman animals, embryos, permanently unconscious persons, or profoundly demented persons) from being considered ethically.

According to Dieter Birnbacher (2006), the concept of a person has become the crucial question ("Gretchenfrage") of contemporary bioethics, but it paralyzes ethical debates more than it inspirits them. The extreme positions of the "personhood" debate are on the one hand the "equivalence doctrine" ("person" equals "human being"), on the other hand the "non-equivalence doctrine" (the set of "persons" does not equal the set of "human beings"; i.e., some human beings are no persons, whereas some persons are no human beings). Birnbacher

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[15] Dirk Hartmann and Thorsten Galert are the principal authors of the relevant chapter (Chapter 5, pp. 189-287) of Merkel et al. 2007.

has convincingly argued that both positions would be better off without the concept of personhood: The equivalence position is threatened by the fact that some human beings lack certain capabilities which are necessary conditions of personhood (e.g., permanently comatose individuals, anencephalic newborns). Its proponents use several strategies for immunizing the position against this fact, particularly arguments against the necessary actuality of these capabilities, identity arguments, as well as individual or species-based potentiality arguments. But these strategies just dissolve the connections between personhood and the capacities which define a person. On the other side, the non-equivalence doctrine does not need the concept of a person for prescribing moral rights to certain individuals, since it founds moral rights mainly on the capacity for feeling, and not on capacities which define persons. Birnbacher argues convincingly that the term "person" is cryptonormative and misleads to understand it as a descriptive term. The abandonment of this term would free the way for more fine-grained analyses and justifications of moral rights (ibid., pp. 53-76).

Martha Farah and Andrea Heberlein (2007) argue in the same vein: Although personhood is a foundational concept in ethics, it is not possible to define it in psychological and neurological terms in a both specific and non-arbitrary manner, since the concept of person does not correspond to any real category of objects in the world.

For the issue of changes in personality after brain interventions or lesions, the concept of personhood is prima facie not relevant, since even after dramatic personality changes, it is not questioned whether the person is still a person, but whether she is still the same person. However, the bioethical discussion about changes in personality after interventions in the brain deals with the question of "loss of personal identity" and "death of the person". In the words of Hartmann and Galert: "the case that a person is annihilated because constitutive conditions for personhood no longer obtain needs to be distinguished from the case that a person is annihilated because of a change of personal identity" (Merkel et al. 2007, p. 211 f.).

According to suchlike concepts of a person, a human being can suffer three different kinds of death: (1) biological death of the human being (e.g., after irreversible cardiac arrest); (2) psychological death because personhood is finished (e.g., persistent coma); (3) psychological death of the person because of a change of personal identity, whereby a new person comes into existence (e.g., after retrograde amnesia and/or severe change in personality).

The latter case is object of recent bioethical discussions about the possible loss of personal identity after interventions in the brain.

Personal identity

In philosophy, there exists an amount of literature about personal identity (overviews: Hartmann & Galert in: Merkel et al. 2007, Chapter 5; Olson 2010; Shoemaker 2012; Stier 2006, pp. 20-40). The Analytic tradition of philosophy is dominated by neo-Lockean psychological continuity theories of identity. According to Lockean theories of person, the persistence of a person depends on the persistence of the capacities which define a person, namely on certain psychological and practical capacities, e.g., memory, moral agency, reflective self-consciousness, and the ability to act on reasons. The persistence conditions of persons are psychological, in contrast to the persistence conditions of human beings which are biological.

According to Olson (2010), the "persistence question" of a being is the question "what is necessary and sufficient for a past or future being to be X"; this is the question about numerical identity. Two persons are *numerically identical*, if they are one and the same person at different moments. Numerical identity is different from *qualitative identity.* Qualitative identity of two objects is given, when they are exactly similar; e.g., identical twins may be qualitatively identical, but not numerically identical, as there are two of them. Obviously, people do not remain qualitatively the same throughout their life, since they change in many physical and mental regards. Nevertheless, a person remains numerically the same for as long as she exists (*temporal persistence* of a person). The persistence question is *not* the question about qualitative identity (What does it take for someone *to remain the same person* over time?).

The Analytic tradition in philosophy has focused on numerical identity. It has developed several thought experiments in order to explicate issues of personal identity. Most of them deal with the section, copying, fission or transplantation of heads, brains, or mental states.

The persistence criteria of personal identity have been grounded on different criteria, which can be roughly divided into physical and psychological criteria.[16] The choice between a physical and a psychological criterion mirrors the distinction between a materialistic and a dualistic ideology (Brand 2009). Both accounts have trouble with different thought examples (the psychological account with fission cases, the somatic approach with brain transplantation cases, as described in the following). Finally, the decision for the one or the other approach depends on general metaphysical considerations (Olson 2010).

1. Physical criteria of personal identity

(a) Somatic approach: According to the somatic approach to personal identity ("*Animalism*", e.g., DeGrazia 2005a; Olson 1997; Williams 1970), the identity of human beings through time consists in some physical relation. Whether people survive or perish has nothing to do with psychological continuity but only with the survival of the human animal, since we are essentially human animals, not persons. In a nutshell, this approach states: Just one person per body. This implies first the impossibility of several persons inhabiting one body (neither sim-

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[16] Besides the physical and the psychological approaches, there are several intermediate positions (e.g., Northoff 2001; Shoemaker 2012; overview: Northoff 2001).

ultaneously nor consecutively). Second, it excludes the transfer of a person from one body to the other (neither by soul wandering nor by copying the whole mental state by a science fiction machine). Third, it excludes that persons can survive their bodies (neither in afterlife, nor stored on a computer system). – The main objection against Animalism is the thought experiment of brain transplantation: If the brain (or the cerebrum) of a human being is transplanted into the body of another human being, then the person goes with the brain, i.e., after transplantation, the person is located in the body into which the brain has been transplanted, not in its original body. – I think that this objection is only partially right, since its assumption that the person is located exclusively in the brain, whereas the "rest" of the body is only the supporting machine of the brain, is too narrow. This traditional hierarchical brain-body model neglects that not only the brain controls the body, but also the body influences the brain through many metabolic processes; thus the body also influences the mental state. For example, thyroid dysfunctions can cause psychosis (Skuster et al. 1992); which certainly affects the person, including her legal responsibility. Therefore, the idea of transporting the person from one body to another by transplanting the brain is too coarse. It has to be anticipated that the transplantation of a whole brain into another body would have relevant effects on the brain, so that the mental states would be modified, perhaps so significantly that the person would be changed.[17]

(b) Brain-based approach: According to the objection to the somatic approach, personal identity has been grounded on the identity of the brain (Wiggins 1980); this is considered as a both necessary and sufficient criterion of personal identity by Nagel (1986). – This approach has been criticized with another thought experiment (Williams 1973): If all parts of the brain were consecutively replaced by technical devices and if all mental functions were preserved during this process, then the identity of the person was saved, although the identity of the brain was not preserved. – However, this objection is based on biological unsound prerequisites, namely a computer model of the brain that wrongly presupposes a complete independence of mental states from their physical basis. Nevertheless, this objection points out that not the material identity of the brain, but rather its functional identity is relevant; this could indeed survive certain modifications of the material substrate.

(c) Biological approach: Michael Quante (2002) argues that neither body- or brain-based nor psychological criteria alone suffice for establishing personal identity. Rather, the whole human organism, including the mental states, establishes the personal identity of human beings. According to Quante, the persistence of a person is identical to the persistence of the

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[17] This idea has been convincingly enfolded in Charlotte Kerner's novel "Kopflos" (2008). She describes the transplantation of the head of a severely injured man to the body of a brain-dead man. The resulting person is neither identical with the head-donor nor with the body-donor, but combines traits from both and gradually develops a new self-concept ("identity") as a new person that has been created in the transplantation process.

human individual. For analyzing the persistence relation, the concept of a person is not necessary. Rather, the persistence of human individuals is determined by the biological laws that are relevant for members of the human species. Psychological functions can be integrated in the biological approach, but they are no necessary conditions for the persistence of human individuals (Quante 2002, pp. 54-60).

2. Psychological criteria of personal identity

Most authors from Analytic Philosophy define personal identity mentalistically or psychologically. According to the different psychological approaches, some sort of psychological relation is necessary and/or sufficient for the persistence of a person.

(a) Personal identity based on memory: Locke has suggested the sameness of consciousness as the criterion for personal identity, which is based on the continuity of the episodic memory (Locke 1690: II.XXVII, § 23, pp. 216-217). According to this approach, following a complete retrograde amnesia, a new person comes into existence in the affected human being. Consequently, this new person should not be sued for criminal deeds the "former person" had committed. This position is not compatible with law: A defendant with complete retrograde amnesia would not be seen as a new (and innocent) person, but as someone with a mental disorder (dissociative amnesia) (see Hartmann & Galert in Merkel et al. 2007, pp. 269-271).

(b) Personal identity based on psychological connectedness or psychological continuity with the right kind of cause: Derek Parfit's theory has probably the greatest influence on the recent bioethical debate about brain diseases and interventions which potentially change the personality. Parfit has conflated qualitative and numerical identity: "Indeed, on one view, certain kinds of qualitative change destroy numerical identity. If certain things happen to me, the truth might not be that I become a very different person. The truth might be that I cease to exist – that the resulting person is someone else." (Parfit 1984, p. 202). He argues that what matters in survival, is not personal identity, but psychological connectedness and/or psychological continuity with the right kind of cause ("relation R") (ibid., p. 215).[18] Particularly, memory is a prerequisite of psychological connectedness; therefore severe dementia is a condition which could cause the "death" of a person (while the individual is biologically alive).

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[18] Parfit's thesis that identity does not matter in survival is based on the fission thought example: "My body is fatally injured, as are the brains of my two brothers. My brain is divided, and each half is successfully transplanted into the body of one of my brothers. Each of the resulting people believes that he is me, seems to remember my life, has my character, and is in every other way psychologically continuous with me." Parfit asks: "What happens to me?" and answers that only four possibilities exist: "(1) I do not survive; (2) I survive as one of the two people; (3) I survive as the other; (4) I survive as both." He refuses answer (1): "double survival" is not death. Answers (2) and (3) are rejected since they violate the transitivity requirement. (Because of the transitivity of identity, both brothers would also have to be identical to each other; but because they will develop differently, this is wrong.) The right answer is that I survive as both. Parfit concludes that Relation R takes a branching form, whereas personal identity cannot take a branching form. Personal identity just consists in the holding of relation R, when it takes a non-branching form. What matters in survival, is relation R (which can take a branching form) (Parfit 1984, pp. 254-263).

Psychological continuity (defined as overlapping chains of strong connectedness) is destroyed if more than half of the connections that hold over any day are destroyed (ibid., p. 205), e.g., by brain trauma. Since Relation R is a matter of degree, survival is a matter of degree, too.

(d) Narrative identity:[19] Besides Parfit, Marya Schechtman has a great impact on the bioethical debate on personal identity. Schechtman (1996) differentiates between numerical identity (issue of re-identification) and narrative identity (issue of characterization of a person). Narrative identity involves an individual's self-conception, i.e., her most central values, implicit autobiography, and identifications with particular people, activities and roles. The concept of narrative identity has a large intersecting set with prevailing models of personality of psychology and psychiatry, but goes beyond insofar it comprises additional features of persons which are not registered by psychological standard tests, namely those related to a person's biography and purpose in life. The narrative identity can be modified by experiences, psychiatric drugs, brain interventions, and neuroplastic processes (Focquaert & DeRidder 2009). Schechtman (2010) denies the existence of a sharp division between person-specific concerns and biological facts. Rather, she suggests a "person-life view": A person is a being that lives a person-life, i.e., the kind of life typically lived by an enculturated human; a single person continues for the duration of a single person-life. Therefore, a severely demented individual is the same person as the pre-dementia person, not simply because she is the same biological being, but because she is the same person in ways that have immediate practical implications since "a 'residue' of the implications of the Lockean capacities remains even when those capacities are lost" (ibid., p. 278).

(e) Narrative approach to personal identity: Hartmann and Galert (Merkel et al. 2007, pp. 249-272) have developed an understanding of personal identity which is based on a narrative approach to personality and focuses on the self-concepts of persons. They argue that "character" can be ascribed also to beings which are not persons (e.g., animals or babies), but the concept of "personality" expresses a qualitative difference due to the fact that persons are self-referential beings, who do not only have character traits, but, moreover, hold a set of beliefs about these traits. The self-concept of a person is constituted only by those beliefs about her own personality traits that she honestly considers to be true. Persons create their self-concepts by telling coherent stories of how they came to be who they are. Since the self-concept is an integral part of a person's personality, persons create their own personality in a limited sense as well. Hartmann and Galert emphasize the relevance of social processes of interpersonal exchange in which self-concepts are constituted: A person's "*personality* is what is represented in the most *intersubjectively convincing* story of who that particular person ac-

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[19] The concept of "narrative identity" has been developed by Paul Ricoeur (1991).

tually is when compared to others" (ibid., p. 259). Within this conceptualization, "personality changes" and "changes of personal identity" do not coincide: Persons can persist through very profound changes of their personality, i.e., their character-traits (temper-traits, motifs, propositional attitudes and talents) and their self-concepts (ibid., p. 264). Even a significant change in a person's personality does not necessarily turn her into another person. This has forensic implications: If a defendant argues that "he emanated from a change of personal identity, so that 'he is no longer the person' who committed the felony, this is no valid way out: Even a drastic character change alone is no sufficient condition for a change of personal identity (ibid., pp. 269-271). Even a massive intervention in the brain resulting in a brain that is not the same anymore does not necessarily destroy personal identity, if the crucial psychic functions are preserved (ibid., pp. 276-277). The relevant criterion for the persistence of a person is after all, whether the person can plausibly integrate personality changes (including changes of her self-concept) into her ever developing self-concept (ibid, p. 279).

Impact of the debate on personal identity for ethical issues of interventions in the brain

Both Locke and present-day neo-Lockean theorists assume an intimate connection between personal identity and ethical issues (Schechtman 2010). Schechtman argues that although neo-Lockean and animalist approaches yield opposing results in many bioethical questions, their difficulties can both be linked to the Lockean conception that they hold in common: In this conception, a sharp distinction is drawn between presumably unique human capacities ("person-making capacities") and "animal features", which humans share with other animals. Whereas for neo-Lockeans two distinct entities result (namely persons and human animals), for animalists a sharp division is drawn between practical concerns that go with personhood and mere metaphysical facts that go with animality.

David DeGrazia (2005b) has criticized that most of the philosophical literature on personal identity conflates numerical identity and narrative identity, and thus confounds moral reasoning. This holds particularly for Parfit, who has stated explicitly that "certain kinds of qualitative change destroy numerical identity" (Parfit 1984, p. 202) — a view with far-reaching consequences in bioethics. With regard to neuroenhancement, DeGrazia makes clear that the sense of identity at issue is narrative identity, not numerical identity: Taking an SSRI might change an individual's personality; then the individual is changing, but it is not destroyed and replaced with another person. DeGrazia argues that personality should not be regarded as an "untouchable characteristic" (as Elliott suggests); deliberately changing one's personality is not inherently problematic. He supposes that the tendency to believe one's personality must not be changed stems from a failure to distinguish numerical and narrative identity.

Some bioethical authors abstain from the term “personal identity” and use instead terms as “narrative identity” (Focquaert & DeRidder 2009; Müller O et al. 2010; Schechtman 1996), “narrative approach to personal identity” (Hartmann & Galert in Merkel et al. 2007, pp. 259-271), “individual identity” (Olson 1997; Witt K et al. 2012 and 2013), “human identity” (DeGrazia 2005a+b), “biographical identity” (Quante 1999) or “relational identity” (Baylis 2013). This variety further complicates the debate about threats to identity by interventions in the brain.

In the following, I will not discuss the theories about personal identity *philosophically*; rather I want to investigate the consequences of their transfer from philosophy of mind to real-life issues of medicine *ethically*. For that, I will discuss several bioethical papers in which Parfit’s theory or other concepts of personal identity have been used to argue about neuroethical or legal issues: first for criticizing advance directives; second for questioning interventions in the brain which could change the personality, e.g., DBS or intracerebral stem cell transplantations; third for a plea against aggressive treatments of malignant brain tumors if the patient’s personality is at risk.

1. Example: Advance directives for severe mental disability after brain damage

World-widely known is the case of Terri Schiavo, the young woman who suffered from an apallic syndrome after a cardiac arrest. For the sake of argument, I assume that she had demanded in an advance directive to let her die in case of an irreversible apallic syndrome.[20] Should this demand be fulfilled? Two fundamentally contrary answers have been given:

- **Yes:** $P_1 = P_2 \rightarrow P_1$’s autonomous will should be respected.[21]
- **No:** $P_1 \neq P_2 \rightarrow P_1$ cannot decide for P_2.

Legally, Terri Schiavo was one and the same person before and after the brain damage. In Germany, her advance directive had to be followed if certain conditions were fulfilled. Nevertheless, this straight-forward answer has been criticized by referring to the second position. According to this argument, Terri Schiavo before the brain damage, called P_1, has no right to decide about life and death of Terri Schiavo after the brain damage, called P_2. The idea that the formerly autonomous person is not the same person as the now-nonautonomous, e.g., demented or comatose, patient is sometimes brought forward for questioning the legal position of advance directives, since they often express the demand for active or passive euthanasia. In neuroethics, the idea that after a drastic change in personality a person is replaced by another person is inspired by thought examples of the philosophy of mind and psychological continuity theories of personal identity. Parfit’s theory has been used to discuss the general availabil-

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[20] Although she did not have an advance directive, she had – according to her husband – stated that in such a case she did not want that her life would be prolonged artificially.

[21] P_1 = person before brain damage, P_2 = person after brain damage.

ity of advance directives (Buchanan 1988; Buford 2008): If a person is defined by certain psychological criteria and ceases to exist when the psychological continuity and/or connectedness is disrupted by a given event, then any advance directive written before that event becomes inapplicable for the person after this event, since the former person has no right to decide about the future of the new person – just because the latter is a distinct person (*Slavery Argument*) (Buchanan 1988)[22] or a non-person (*New Slavery Argument*) (Buford 2008). Buford (2008) has deduced that psychological theories of personal identity have the consequence that advance directives are senseless and invalid in general: Since advance directives are always written by competent persons, who have 'ceased existing' and are 'replaced' by incompetent persons or by non-persons at the very moment the advance directive should be applied, it could not be applied according to this theory.[23]

Reinhard Merkel (1995, p. 566) has published a thought example which illustrates the case of severe mental disability after brain surgery: A is a devout Jehova's Witness. He suffers from a brain tumor, and before surgery, the physicians inform him about the risk of a severe mental disability after surgery. A writes therefore an advance directive in which he forbids any blood transfusions for the future. Indeed, after surgery, A is severely mentally disabled; he is comparable to a child one year of age, but enjoys his life. When he has an accident, he could be easily rescued with a blood transfusion. Should the physicians respect his advance directive and let him die, or should they disregard it in order to save his life? Merkel argues that it is morally inacceptable to let A die; although it confirms to German law. He argues neither with a Pro-Life position nor with the beneficence principle but with an argument inspired by Parfit's theory: Between A1 and A2 does no sufficient mental identity exist. Therefore must A1 not decide about life and death of another person A2. The only bodily identity of A1 and A2 does not suffice to suppose a mental identity between the two persons, when a complete and irreversible disjunction of their consciousness has occurred. Nevertheless, Merkel does not demand to ignore advance directives in cases of irreversibly lost autonomy; rather he demands to weigh the former personal preferences against the present and future interests of the patient.

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[22] Buchanan (1988) accepts the psychological theory of personal identity, but refuses the slavery argument as "invalid or, if modified to achieve validity, unsound". He suggests a compromise position which "acknowledges both the value of our current institutions and practices, which to a large extent do treat personal identity as an all-or-nothing affair, and the implications of the view that personal identity depends upon […] psychological continuity which admits of degrees" (p. 298). He argues that a person who issues an advance directive may do so also to protect certain interests she has in what happens to her body, after she no longer exists (as a person). He concludes that advance directives are applicable in case that a person becomes a "nonperson", e.g., a profoundly demented individual.

[23] Buford (2008) confesses to Animalism, according to which "our persistence conditions are non-psychological in virtue of the fact that each human person is numerically identically to a human animal" (p. 424): "My own view is that Animalism is correct; hence, any psychological account of our identity over time is incorrect." (p. 430).

The persuasive power of Merkel's thought example depends strongly on the special case of the religious denial of lifesaving blood transfusions. We are obliged to accept this case as an example of an autonomous decision despite of its irrationality, since even the most irrational ideas do not count as delusions in the psychiatric sense if they are part of an established religious belief. Nevertheless, nearly all people would be relieved that the brain injury has erased the irrational religious ideas, and therefore most people would easily accept arguments for overriding the officially autonomous, but actually foolish decision.

In order to avoid this bias, I suggest to turn Merkel's thought example the other way round: B is the atheistic son of devout Jehova's Witnesses. He suffers from a brain tumor, and before surgery, the physicians inform him about the risk of a severe mental disability after surgery. Therefore, B writes an advance directive in which he demands for blood transfusions if necessary – explicitly against the will of his parents who would be his legal custodians. Indeed, after surgery B is severely mentally disabled; he is comparable to a child one year of age, but enjoys his life. When he has an accident, he could be easily rescued with a blood transfusion. Should the physicians respect his advance directive and save his life or should they disregard it in order to respect his parents' substitute decision? Since B2 is a non-autonomous person, virtually again a minor and dependent child of his parents, his wellbeing is defined substantially in relationship to his parents. Therefore, not B1's advance directive should be regarded, but B2's parents' substitute decision. According to Merkel's adaptation of Parfit, it follows: Since no sufficient mental identity exists between B1 and B2, B1 must not decide about life and death of another person B2. The only bodily identity of B1 and B2 does not suffice to suppose a mental identity between the two persons, when a complete and irreversible disjunction of their consciousness has occurred. Probably most people (except strong adherers of relational ethics or of parental rights) will find this result of the Parfit-application immoral, because a mentally disabled person would be sacrificed to an irrational religious principle which he neither understands nor believes in. Furthermore, this result is not comparable with German law; in this case, a family court would abandon the parents' custodianship for this medical decision in order to protect the life of the dependent person.

Comparing the two thought examples makes clear that the application of advance directives is not principally ethically problematic, but only if their contents are either irrational or immoral so that their application would conflict with ethical principles.

If the legislator would accept the metaphysical idea that a person can be replaced by another person through certain events, which disrupt her psychological continuity and/or connectedness, and its logical consequence, that advance directives are invalid in general, then a backlash would occur to the time before the legislation about advance directives. Citizens would be denied again the right of making autonomous decisions for their own future, including possible states of altered or lacking consciousness. Maybe more education is needed about the pitfalls of advance directives and the expectable quality of life in different conditions; but the solution should not be a revival of paternalism, this time Parfit-based.

The application of Parfit's theory would have bizarre consequences in criminal law, too, as the following thought example illustrates: The convicted child rapist and murderer Dutroux suffers an epileptic seizure in his temporal lobes; thereby he sees God. He becomes a believer and now, he condemns rape and murder, and hardly remembers his crimes. He says: "I have found to God: I am no longer the person I used to be. I am a new person: Dutroux*. I am not responsible for the crimes of Dutroux." Dutroux* could rely on Locke who has argued that someone should not be held accountable for actions that he cannot remember (1690, II.XXVII, §§ 19-27, pp. 214-219). He could also refer to Parfit, and argue either that the epileptic seizure had disrupted his psychological connectedness, or that it had deleted or changed more than 50% of his memories, beliefs, and intentions. If this claim would be true, Dutroux* should be released from jail: Dutroux* must not be held responsible for another person's, namely Dutroux's offences.

Although this argumentation looks absurd from a legal perspective, David Shoemaker claims that "when a hardened criminal is genuinely converted to Christianity while in prison, there are many who would advocate absolving him (the 'new' him) of his (the 'old' his) crimes" (2008, p. 7). However, law is based on animalism. "There can only be, then, in the eyes of law, just one person per body" (Shoemaker, 2008, p. 233). Neither retrograde amnesia nor a significant personality change can abolish the legal responsibility. As Schechtman (2009) rightly emphasizes, our practices of promising, contracting and assessing praise or blame depend on the notion of personal identity, but in no way on personality. Therefore an imprisoned murderer who has experienced a religious conversion and become a pacifist is not thereby absolved of responsibility for his criminal behavior (Baylis 2013).

2. Example: Loss of personal identity after DBS or intracerebral stem cell transplantation

Recently, the application of the concept "loss of the personal identity" has been extended from non-autonomous persons to Parkinsonian patients under DBS, who are temporarily either (hypo-) manic or apathetic (Glannon 2009; Schechtman 2009; Witt K 2013), and to Parkinsonian patients treated with intracerebral stem-cell implantation (Goldstein 2011).

For Marya Schechtman (2009), DBS for Parkinsonism is a potential threat to personal identity, since it can change personality, passions and interests. She thinks that a Parkinsonian patient who developed very different passions and commitments after DBS has "(in at least some respects)" "become a different person". Although he has to be seen "as a forensic person post-DBS”, it is “hard to see him as the *same* forensic person as before DBS”. According to Schechtman, the relevant factor is the *cause* of the patient’s “change of heart”, namely in this case, the fact that the change was not caused by something he has seen, learned or reconsidered, but is the effect of direct electrical stimulation to the brain. The sticking point is that “the way in which [his] psychological makeup depends on biological factors is different from the ordinary case”. Therefore, the crux is whether a personality change is caused by technical manipulation of the brain or by natural personal development. Schechtman opines that a personality change caused by technical intervention is at odds with either the “articulation constraint” (which requires the ability to articulate one’s narrative and to explain why one does something) or the “reality constraint” (which requires that an identity-constituting self-narrative should fundamentally cohere with reality) (ibid., pp. 76-86).

But although this argument looks intuitive, it is not convincing: A person whose personality has been significantly changed by DBS could satisfy the articulation constraint by including a description of consent to DBS in her self-narrative and thus integrate the change into her autobiographical narrative (Baylis 2013). Furthermore, the person could add descriptions of her experiences with the stimulation, of her reflections about stimulation-induced personality changes, etc.; in this way, the technically induced personality change would become more and more part of her self-narrative.

Walter Glannon (2009) states that for DBS-induced changes in personality the “concept of identity at issue here is not numerical identity”, but “narrative identity” as defined by Schechtman (1996). Glannon remains ambiguous with regard to the temporal persistence of the personal identity of DBS patients who become manic under stimulation. On the one hand, he argues that a person who undergoes a change from a non-manic to a manic state may have “enough psychological continuity and narrative integrity” to remain the same person “in a weaker yet sufficient sense of identity”. On the other hand he asks: “But how much change in one’s mental states can an individual undergo and remain the same person? How much disruption can one’s life narrative accommodate without threatening the integrity of the whole? Is there a threshold of continuity and integrity below which alteration of the psyche is substantial enough to alter the identity of the person? […] If the mania alters the general content and disrupts the integrity and continuity of his desires, beliefs, intentions and emotions, then the PD patient seems to become a different person once the stimulator is turned on.”

Despite his concerns regarding the risk that a patient might “become a different person” under DBS, Glannon concludes that it is the competent patient who has to decide whether the trade-offs between the physiological benefits of DBS and the potential psychological harm would be acceptable. He emphasizes that not every patient would prefer an “alteration of his self resulting in less suffering" to "a self with more suffering"; obviously he sympathizes with the second alternative. But finally, he subordinates the "metaphysical and psychological questions of identity" under "the normative question of benefit versus harm". In this way, the risk of "becoming another person" can be considered as a potential harm, which has to be weighed against the expectable benefits.

With the subordination of the metaphysical question under the ethical question, Glannon comes in the end to a solution which gives priority to the patient's autonomous decision-making about benefits and risks of a therapy. Despite his skeptical view on possible "alterations of the mind" caused by DBS, Glannon does not plead for forbidding or restraining the use of DBS, even in cases of stimulation-induced mania and loss of decisional capacity.

Karsten Witt and his coauthors regard "the risk of becoming another person following surgery" as "alarming for patients, caregivers and clinicians" and as "one of the most urgent conceptual and ethical problems" of DBS for Parkinson's disease (Witt et al. 2013). Witt has analyzed comprehensively the change of identity thesis with regard to DBS (Witt et al. 2012 and 2013; Witt 2013). Particularly, he asks whether DBS-induced alterations concern the numerical identity or the narrative identity of patients. He rightly states that many philosophers and most bioethicists reject the metaphysical interpretation of personal identity (Witt 2013). Nevertheless, he investigates en detail the metaphysical interpretation of the narrative of "being no longer the same person" after DBS, i.e., the thesis that an individual might not only be changed qualitatively by DBS, but becomes a distinct person. Finally, Witt and his coauthors avoid committing themselves to the metaphysical interpretation.[24] They discuss, but do not explicitly subscribe the thesis that the numerical identity of a person might be changed through DBS. Explicitly they opine only that a person might become a different person in the characterization sense after DBS; i.e., that DBS could change a patient's "individual identity". They emphasize this might even occur if the patient's personality as understood in psychology and psychiatry has not changed significantly. For elucidating this idea, they state that Saulus has become another person, namely Paulus, in the characterization sense, insofar as his central projects, values and beliefs have been changed, although his personality might not have been altered significantly.

Although Witt and coauthors are officially agnostic on the metaphysical interpretation of the change of personal identity thesis, Witt (2013) deduces an ethical demand, which is inspired by the metaphysical thesis that the person after DBS is a distinct person: He demands that consent to DBS has to be given both by the preoperative person and the postoperative

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[24] Witt et al. (2012) leave the question open whether the person has become another person in the metaphysical sense (p. 223, footnote 6.). — Witt (2013) does neither confess to the metaphysical interpretation of change of personal identity thesis, nor does he refuse it, but he obviously sympathizes with it.

person, since both persons would be concerned by the consequences of surgery. Therefore Witt extends the requirements of informed consent as follows: A patient's consent to a DBS treatment which might change his/her character[25] can legitimate this intervention only if the patient (1) accepts preoperatively surgery-related and other medical risks as well as the change in character; and (2) evaluates and weighs the effects of the intervention from his/her successor's perspective, e.g., by asking himself/herself: "How will I* experience these effects?", and if the patient consents to the therapy from this perspective (ibid., p. 14 f.).

Since most bioethicists reject the metaphysical interpretation of personal identity change, Witt supports his demand for extending the requirements of informed consent by a further, merely ethical argument: Since the consequences of the treatment have to be experienced by the postoperative person who might be qualitatively changed, but normally still autonomous, the patient should consider how she would evaluate the consequences from her expectable postoperative perspective.

Since I reject the metaphysical interpretation, too, I do not agree with Witt's demand for an extended informed consent (i.e., both from the perspectives of the preoperative and the fictional postoperative person): If the patient before and after DBS is the same person (whose personality and/or central projects, values and beliefs might be changed), then the informed consent of the pre-operative person is sufficient ─ as for each surgery. It is a good *advice* for patients to consider whether they could accept that their personality could be altered by neurosurgery, and to imagine how they would evaluate the consequences of the intervention if this would happen indeed. But first, it is extremely difficult if not impossible to imagine all possible changes in personality or "individual identity", and then to evaluate all possible consequences of surgery from the perspectives of all possible future personalities. Second, patients cannot be *forced* to consider these difficult questions; physicians might advise them to do so, but allowance for surgery cannot depend on complicated reflections of all eventualities.

Instead of urging patients to reflect about possible changes in personality or individual identity, it makes more sense to plead for better informing them about suchlike consequences of DBS and to support them in considering this information.

To my knowledge, no scholar has officially supported the thesis that DBS could change the numerical identity of patients, although several authors discuss it with more or less sympathy. Nevertheless, I want to hint to an ethically problematic consequence of the metaphysical interpretation of change in personal identity: If legal theorists and physicians would really regard patients, who show after DBS certain personality changes or changes of the personal/individual/narrative/relational identity (e.g., mania, apathy, loss of formerly important in-

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[25] Witt uses here the German term "Wesen" (character); it seems to cover what he has subsumed elsewhere under the term "individual identity".

terests or social relationships), as new persons, then Ulysses contracts written before DBS would have to be regarded as inapplicable. Even if a patient stipulates in a Ulysses contract that in case of stimulation-induced mania the stimulation has to be switched off, even against his present will, this stipulation would have to be ignored – no matter whether he would be legally incompetent or not, just because he would be regarded as another person than the person who has written the Ulysses contract. This would restrict the self-determination of patients for possible future states of incapacity caused by stimulation- or drug-induced mania or psychosis.

In contrast, many bioethicists support psychiatric advance directives as a means of strengthening self-determination of patients (e.g., Feinberg 1986; Quante 1999; Spellecy 2003; van Willigenburg & Delaere 2005;[26] Winston et al. 1982). However, as Rebecca Dresser (1982 and 1984) has argued, the application of Ulysses contracts on persons, who are acutely mentally disordered, but competent, is ethically and legally problematic for a number of reasons. Of particular interest is that Dresser has criticized Ulysses contracts as an instrument of "self-paternalism", whereby she refers to the notion of "the past self" and the "present self". Quante (1999) has convincingly argued that categorical objections to Ulysses contracts based on assumptions about personal identity (as Dresser's) are flawed since they conflate persistence and biographical identity.

Ulysses contracts can legitimate coercive treatments of legally competent persons, only if explicit legislation regulates this situation. Whereas more and more US states are passing laws in favor of this,[27] comparable laws do not exist in Germany. Here, psychiatric advance directives may be applied only to legally incompetent persons.

Nevertheless, Ulysses contracts can be used without legal problems to deal with the risk of adverse mental effects of DBS. Therefore, Markus Christen, Henrik Walter and I have supposed a Ulysses contract that permits to discontinue the stimulation in case of mania or behavior dangerous to the patient himself or to others. Switching off the device or not switching it on again or reducing its voltage, is not comparable with coerced treatment but with not prescribing another dose of drugs because of severe risks or side effects, although the patient demands for them. Therefore, this instrument is legally not problematic ─ in contrary to those Ulysses contracts which permit coerced treatment against the present will (Müller & Christen 2011; Müller S et al. 2013). Rather it is a tool to strengthen the patients' autonomy, to protect

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[26] Van Willigenburg & Delaere (2005) argue that Ulysses contracts cannot protect mentally disturbed patients from the loss of autonomous self-control, i.e., they cannot restore autonomy as sovereignty, but they can protect autonomy as authenticity by upholding the guidance provided by the patient's deepest concerns.

[27] In 2003, seventeen US states had regulations for psychiatric advance directives, which very closely resemble Ulysses contracts as they permit treatment before the criteria of dangerousness (which could justify coerced treatment) have been met (Spellecy 2003, p. 374).

them from negative consequences of manic or psychotic behavior, and finally, to allow them at least partly to prevent undesirable changes in personality.

Parfit's concept of personal identity has been used by Jan Goldstein (2011) for an ethical investigation of intracerebral stem cell implantations for the treatment of Parkinson's disease. Goldstein starts with the nonmaleficence principle and the assumption that treatments which change the patient's identity harm the patient to death, since the survival of a person requires the persistence of his identity. Then he recapitulates Parfit's thesis that identity is not what matters in survival, but psychological connectedness and/or psychological continuity with the right kind of cause. Goldstein deduces from Parfit's theory that if intracerebral stem cell transplants would cause significant changes of psychological connectedness, then one could claim that the patient would not survive the treatment. Goldstein thinks that in the treatment of Parkinson's disease such extensive changes in connectedness are unlikely; and that even in severe cases of stroke, in which large parts of a hemisphere would have to be replaced by stem cells, this condition would not be met easily. But even if psychological connectedness would be broken, Goldstein appeases, we would have to "decide for ourselves whether we would see enough connections or not" and "could at the very least claim that the former person has survived to some degree and partly continues to live on after the surgery" (ibid., p. 54). Finally, Goldstein concludes that "even the most extreme cases shouldn't be seen as equivalent to death"; therefore the initial verdict against a treatment which might change the patient's identity is replaced by the conclusion that the choice about transplantation is "not a choice between survival and death, but rather between two different outcomes". This is a trivial statement which could have been gained without Parfit's complicated construct of ideas.[28]

After investigating these philosophical papers on possible changes in personal identity following DBS or intracerebral stem cell implantation, a look to the patients' perspective is demanded. Indeed, this challenges the concerns of the philosophers discussed above: Northoff (2004) concludes his questionnaire-based investigation of Parkinsonian patients, who had been treated with either DBS or stem cell implantation, that "they did not experience changes in their personal identity since they were able to psychologically integrate the implant within their experience in First-Person perspective", although they showed changes in their personality. These empirical findings support the thesis that metaphysical ideas of "loss of personal

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[28] An empirically informed ethical analysis of intracerebral stem cell transplantations, which is not based on theories on personal identity, has been performed by Elisabeth Hildt (1999 and 2009). — Northoff (1996) has shown that proponents and opponents of the thesis that brain tissue transplants can alter personal identity, use the same arguments but with different underlying presuppositions. These presuppositions concern the meaning of "identity", either numerical or qualitative, the understanding of brain identity, either structurally or functionally, and the relations between mental states, psychological functions and neurophysiological properties.

identity" are inappropriate for ethical analyses of the issue of possible personality changes following DBS or intracerebral stem cell implantations.

3. Example: Loss of "self-identity" due to brain tumors and their treatment

Generally, neurosurgery does not pay much attention to personality changes of patients. This is valid particular for the treatment of life-threatening conditions as malignant brain tumors. The paper of Lisa Anderson-Shaw, Gaston Baslet, and John Villano (2010) about the potential impact of brain tumors on self-identity addresses this under-recognized problem. The authors doubt the sense of the prolongation of life by modern medicine in cases where the patient's personality has dramatically changed, or his/her "self-identity" is at risk by either therapy or disease progression.

Unfortunately, the authors' perspective is biased: They present exclusively cases in which the treatment prolonged the span of life, but failed to arrest the deterioration of the neuropsychological state and to save the premorbid personality. The biased selection of cases supports the assumption that brain cancer patients are *generally* confronted with the dilemma of choosing either a shorter span of life with a longer time span with their premorbid or pre-operative identity, or a longer span of life with the risk of losing their previous identity. Based on this assumption, the authors demand for limiting therapies and for supplying palliative care rather than aggressive therapies, when there is a strong prognosis of loss of aspects of self. Their argument looks coercive mainly because of one case report: A brain cancer patient became psychotic and nearly killed his sleeping wife because he was convinced that she was allied with burglars. But it has to be noted, that this catastrophic outcome did not occur under therapy, but after the patient's denial of further treatment, and after the physicians had failed to convince him to be seen by a psychiatrist.

Doubtlessly the dilemma of prolonging either the span of life or the time span with the intact personality occurs in some cases. But for the majority of brain cancer patients, this dilemma either does not appear or can be resolved: Reducing the mass of malignant brain tumors and suppressing their growth often has positive effects on both the span of life and the brain functions. The dilemma occurs only if neurosurgery, irradiation or chemotherapy is used too radically. If the treatment aims at functional integrity and is tailored optimally, it can enhance the span of life, quality of life and even personality and behavior.

A non-biased perspective also considers cases in which brain tumors changed the patients' personalities whereas aggressive treatments (resections, irradiation, or chemotherapy) saved or even "restored" the premorbid personalities.

The evaluation of personality changes should be done very cautiously, because the patients' evaluation may differ significantly from the evaluation of physicians and family members. Even more cautiousness is required for attributing a "loss of self-identity". Even if relatives say that the patient is not the same as he used to be, the patient may still have a sense of continuity and of intact self-identity. Some patients are able to value the "new person" and to find a new meaning of life in spite of all reductions and losses (Lucius-Hoene 2008).

Therefore I support Anderson-Shaw and her coauthors' demand for the development of a framework for assessing the "self-identity" of patients with brain tumors or other severe brain diseases. But the necessary respect for the patient's personality should not support therapeutic nihilism; rather it should become an important factor (besides the factors quality of life and survival time) for evaluating whether further treatments make sense (Müller S 2010).

Conclusion

The decision about a brain intervention is an existential challenge, since it is often a decision about life or death, and frequently about possible personality changes. In many cases, the waiving of an indicated brain intervention bears the same risks as the intervention, although mostly with different probabilities and another chronological sequence. The patient has to decide whether he will dare to awake from anesthesia with a modified personality, which might show attitudes or behaviors which would have been quite inacceptable for him prior to the intervention. The patient has to be aware that after the intervention he might lack the capability for autonomy, might have a weak self-control, an insufficient moral competence, a deficient sense of socially adequate behavior, and/or a compromised autobiographic memory, so that the link between the pre- and the postoperative person might be flawed indeed.

Insofar, the papers discussed above have considered an ethically relevant problem. However, the application of psychological continuity theories of personal identity, particularly of Parfit's theory, on these neuroethical issues is misleading for theoretical, ethical and legal reasons:

First, these theories are based on an ontological person-organism-dualism which is obsolete in light of neuroscience. The metaphysical idea that different persons can inhabit one body one after the other, looks like an obscure relict of dualistic philosophies. Thought experiments of the philosophy of mind about the section, copying or fission of heads, brains or mental states are useless for explaining changes in personality and the phenomenon of self-alienation that is reported by and about some neurosurgical patients, since their physical and biological senselessness makes them useless for solving ethical dilemmas in real-life.

Second, the manner of speaking of "loss of personal identity" is based on a static model of persons and of personality. Actually, each person undergoes more or less significant and more or less abrupt changes between birth and death, and the personality is developing throughout the whole life. A static view of personality supports a general negative view on personality changes following interventions in the brain.[29] But as I have argued in Chapter 1, in many cases patients undergo personality changes which are experienced as positive both by themselves and by their social surrounding. Particularly, personality changes, which restore a patient's capability for autonomy that was affected by a brain disease, have to be evaluated positively. Furthermore, from this perspective follows an ethical imperative to support patients to regain their capability for autonomy if it is diminished by diseases.

Third, the use of these theories is misleading for empirical reasons, since the quality and degree of mental alterations which normally occur after neurosurgical interventions do not justify speaking of losing the personal identity; this holds particularly for intracranial stem cell implantation and DBS. Even though some brain interventions cause significant and partly problematic personality changes, questioning the personal identity can be justified at the utmost in such extremely rare cases in which the whole personality is changed and complete retrograde amnesia has occurred.

Fourth, it remains mysterious which circumstances qualify for diagnosing that a person's psychological continuity and/or connectedness is so disrupted that a new person replaces the former one. Although the whole discussion is based on a few case reports, all scholars use different, mostly implicit criteria for diagnosing a change of personal identity. Finally, one will come back to the concept of personality to define what is meant by "change of personal identity" (Birnbacher 1995). And then it would be more elegant to abstain from metaphysical ideas of personal identity loss and replacements of persons in one and the same body. Since the term "identity", even if connected with attributes as "individual", "human", "narrative", or "relational", will always evoke a conflation of numerical identity with some form of qualitative identity, I suggest doing without the enigmatic term "identity". In order to highlight the relevant finding that the term "personality" as defined by psychology and psychiatry does not suffice to capture all significant aspects of an individual's personality, I suggest to dedicate the term "personality" for its use in psychology and psychiatry, and to use different terms for referring to personality as understood either in folk psychology or in philosophy. Concretely, I suggest to use terms such as "character", "personality in the broader sense", "personality and self-concept", or "personality as defined by X" instead of "narrative identity", "individual identity", "human identity", or "relational identity".

Fifth ─ and this is my main concern ─, the transfer of psychological continuity theories of personal identity, particularly of Parfit's theory, to neuroethical issues implicates ethically and legally extremely questionable conclusions. If legal theorists would take these theories seri-

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[29] Annemarie Heberlein (2013) has also criticized the static understanding of personality that underlies the concept of "identity". She has argued for a dynamic concept of the self, in which the development of personalities through experiences and social interactions is an integral element.

ous, this would have fatal legal consequences for patients who undergo interventions in the brain: The denial of advance directives and Ulysses contracts would take away a valuable instrument which helps patients to protect themselves against some of the consequences of intervention-induced incapacity because of coma or de novo psychiatric disorders. This consequence would significantly harm the patients' autonomy and eventually their (mental) health, freedom, social status, and relationships. Furthermore, these theories support therapeutic nihilism for some groups of patients, particularly for brain cancer patients.

Therefore I come to the conclusion that the principle of respect for autonomy is indeed challenged by cases of significant and problematic changes in personality; however, argumentations based on psychological continuity theories of personal identity are misleading, since they are based on dualistic and static concepts of persons and finally sacrifice the respect for autonomy.

Since ideas borrowed from the philosophy of mind are misleading and not useful for solving dilemmas posed by iatrogenic personality changes, another strategy for dealing with these dilemmas has to be developed. To enable neuroethics to better analyze the existential problems of some neurosurgical patients, both empirical research and theoretical work is necessary in order to investigate the following issues:

Neurobiological and evidence-based clinical research: Which brain areas or brain circuits are especially relevant for changes in personality? Are there laterality effects or effects of lesion size? How does the patient's age influence whether personality changes occur and how the patient can integrate them into his or her self-image? What about the reversibility of personality changes and about therapeutic options to influence them?

Psychological research: Are changes in personality a major concern of patients preoperatively?[30] How do patients experience personality changes subjectively? How significant are psychological continuity and psychological connectedness for patients' wellbeing and self-image? How do patients adapt to personality changes in the longer run? In how far are the cause of personality changes (e.g., disease vs. neurosurgery) and their temporal patterns relevant for the ability to adapt to these changes? In how far do reactions of the social surround-

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[30] Empirical knowledge about this question is meager. Only a handful of studies have investigated this issue: Lipsman et al. (2009) found that patients in general did not view "threat to their identity" as a major concern prior to an either microsurgical or radiosurgical intervention to their brains. Almost all participants, when confronted with hypothetical scenarios, chose to proceed with a life-saving or –extending operation, even though the risk to personal identity and personality was significant. Interestingly, patients who would undergo craniotomy, prioritized risks as limb paralysis and blindness to be significantly worse than personality change; whereas in the radiosurgery group a majority of patients found personality change to be the most disturbing risk. The latter patients have very little or no risk to personality, whereas the first group of patients is confronted with this risk.
In our study with acoustic neuroma patients, we found that 11% of the patients who had chosen radiosurgery said that they had decided against microsurgery because of fear of personality changes (Chapter 3; Müller et al. 2010). I guess that patients who are particularly aware and afraid of the risk of personality change through microsurgical interventions tend to decide for radiosurgery, if this option is available.

ing influence the patients' adaptation to personality changes? Do DBS patients feel being manipulated by the physicians who control their stimulation parameters?

Since standard personality tests from psychology and psychiatry are not sufficient to investigate the complex phenomenon of personality changes after brain interventions comprehensively, they should be complemented by qualitative and narrative methods (Krug et al. 2010; Lucius-Hoene 2008; Müller O et al. 2010; Müller & Christen 2011; Witt et al. 2012).

In my view, neurologists in the tradition of Alexander Lurija, Oliver Sacks and Vilayanur Ramachandran can serve as an example for combining scientific medicine, precise and empathetic observation and narrative methods in order to understand and explain such complex cases. Narrative methods can help to investigate subjective and intersubjective issues of personality changes phenomenologically, but a precise description is only a necessary, but not sufficient condition of understanding theoretically and analyzing ethically the phenomena.

7.3 Ethical evaluation of personality changes through brain interventions

For evaluating potentially personality-changing interventions in the brain ethically, the ethical evaluation of personality traits is an indispensable precondition. But modern psychiatry and psychology avoid evaluations of personality traits, particularly ethical evaluations. Nevertheless, evaluations of personality traits are indispensable in order to define goals of treatment and to evaluate the therapeutic response. Modern psychiatry and psychology use pragmatic value measures which are orientated both to the patients' well-being and to social demands. The ethical aspects are masked behind medical terminology.[31] Also personality traits which dispose to harmful behavior are considered rather as "disordered" than as "bad" or "morally wrong". For example, according to DSM-5, a paraphilic disorder is defined as a paraphilia that causes distress or impairment to the individual or *harm to others*.

Louis Charland (2006) has convincingly argued that the neutral clinical descriptive language of the DSM philosophically conceals that moral aspects are an integral part of the DSM conception of Cluster B personality disorders (i.e., antisocial, borderline, histrionic, and narcisstic personality disorders). The defining criteria for these disorders invoke explicit moral terms and notions, e.g., the DSM criteria for antisocial personality disorder include "deceitfulness, as indicated by repeated lying, uses of aliases, or conning others for personal profit or pleasure," as well as "lacks empathy". The moral character is an integral part of the conditions and not logically dispensable (ibid., p. 119).

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[31] However, in medical and psychological publications personality changes are often explicitly evaluated, but without disclosing the basis of the evaluation (e.g., Bridges et al. 1994; Hornak et al. 2003; Hill et al. 1957; Roberts & Mroszek 2008; Sachdev & Hay 1995).

Peter Zachar and Nancy Potter (2010) have argued convincingly that some overlap between the domains of psychiatry and morality is inevitable; they plead for not purging values from science but for finding some agreement with regard to which values should guide psychiatric practice.

For classifying Cluster B personality disorders either as medical disorders or as mere moral disorders, their genesis is a crucial issue. Marga Reimer (2008) has argued that the dominant description of Cluster B personality disorders as “mental disorders”, which are associated with some neurological dysfunctions, is no mandatory description of the empirical facts: Rather, the Cluster B features can be described in a neutral language, i.e., as “different” instead of “disordered”. This could be justified with regard to an evolutionary model, which describes psychopathy as a biological advantage (although the psychopath’s life expectancy is reduced, his reproductive expectancy is above-average). This view is supported by the fact that psychopaths do not have a harmful dysfunction as understood in evolutionary terms.

Although this description of psychopathy (which might be transferred to Cluster B personality disorders) might make sense for “born psychopaths”, it is not useful for describing acquired psychopathy caused by a brain disease (e.g., frontotemporal dementia) or a brain lesion; these cases cannot be classified as *mere* moral conditions.

For interventions in the brain that cause personality changes, which are characterized mainly by behavior harmful to others (e.g., recklessness, hypersexuality, aggressiveness), or even acquired psychopathy, the lines between “mad” and “bad” are blurred. On the one hand, the resulting behavior is morally wrong. On the other hand, the behavior results from disease or has an iatrogenic cause, and the patient is not at all responsible for the changes.

To cause personality changes which are characterized mainly by behavior harmful to others is primarily wrong because of the possible harm for others; and possibly secondary because of harm for the patient. For example, if a patient becomes psychopathic after brain surgery, this will certainly be harmful for other persons, but maybe not for the patient himself, particularly not if his societal position allows him enjoying a psychopathic lifestyle.

Conclusion

In order to evaluate personality changes caused by interventions in the brain ethically, the following criteria should be considered and weighed individually for each patient:

a) Patient-oriented criteria (e.g., conservation or restoration of the capability for autonomy, feeling of authenticity,[32] quality of life, and ability to pursue personal goals)

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[32] Felicitas Kraemer (2013) has convincingly argued for taking the patients’ subjective state of felt-authenticity or felt-alienation into consideration.

b) Criteria related to the immediate social surrounding, particularly the family (e.g., responsibility, reliability, agreeableness)
c) Social criteria (e.g., professional activity, fitness to drive, capacity to contract)
d) Ethical criteria for evaluating the personality and behavior (e.g., respect for others, moral competence, self-control).

7.4 General recommendations for research and clinical praxis of neurosurgery

Although interventions in the brain will always pose an ethical challenge, a number of strategies exist already or have been proposed in order to reduce the number of medico-ethical dilemmas in neurosurgery as well as their severity. In the following, I will summarize the main strategies for assuring the ethical development of (psychiatric) neurosurgery in the form of general recommendations (i.e., neither disorder-specific nor therapy-specific). I agree with Judy Illes (2010) that recommendations for regulations must be pragmatic, flexible, and responsive to the fast-moving science, reasonable for the commercial sector and relevant to the scientific and medical community.

Research

1. Advances in understanding brain functions: In order to intervene effectively in such a complex system as the brain, an understanding of its structure and functionality is essential. Although success in neurosurgery has been based partly on trial and error, this strategy bears significant risks for patients; therefore a main objective of brain research is a better neurobiological understanding of how interventions influence given brain mechanisms and which factors contribute to intended and non-intended effects.

A main objective is to damage brain tissue as little as possible and as much as necessary, and to save particularly tissue in functionally relevant networks. This requires first a deeper understanding of the structures and mechanisms which constitute important brain functions, particularly of the involved neuronal circuits and the most important knots in these circuits. The neuroanatomical networks underlying disturbed neurological or mental functions have to be better understood in order to find optimal targets for interventions and to prevent collateral damage to important structures. Neuroimaging technologies such as fMRI, PET, SPECT, and DTI are invaluable methods for investigating specific brain functions; therefore they can contribute to more precise interventions in the relevant networks, to higher effectiveness and to less risks and side effects. Furthermore, neuroimaging can help to identify targets for intervention, particularly for DBS[33] and (in future) for epilepsy surgery[34].

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[33] E.g., the slMFB has been identified by DTI as a stimulation target for depression (Schläpfer et al. 2013).

2. Minimal-invasive interventions: Interventions in the brain should treat accurately the target area, in order to cure or improve disturbed functions effectively, while the proximate tissue and especially the functionally important structures have to be preserved. The development of both locally precise and target-specific minimal-invasive intervention technologies is of great importance. Examples for locally precise technologies are DBS and radiosurgery (Gamma Knife, CyberKnife, Heavy Ion or Proton Radiotherapy); examples for target-specific intervention technologies are nanotherapies (e.g., application of nanoparticles for hyperthermia treatments of brain tumors or for targeted drug delivery), whose effects are restricted to targets with special biochemical properties where ever they may be localised.

3. Evidence-based evaluation of different therapeutic approaches: Prospective, long-term, if possible, randomized and double-blinded multi-center-studies are needed for comparing different therapy options, particularly their effectivity and efficiency, the incidence and severity of adverse effects, and their effects on quality of life, personality and behavior. By way of example, radiosurgery, fractionated radiotherapy and microsurgery for the treatment of different kinds of brain tumors should be directly compared. In the field of psychiatric neurosurgery, not only the different targets of DBS should be compared for different mental disorders, but also DBS and different ablative methods, particularly radiosurgery. Double-blind-studies are feasible both for DBS and Gamma Knife (Feldman et al. 2001, p. 951; Greenberg et al. 2003). Without such studies, it is difficult to compare the different profiles of benefits and risks of the different methods, and to evaluate their adequateness for individual patients.

4. Case registries and evidence-based evaluation of therapies: Independent case registries are required which contain all clinical studies and all individual treatment attempts, in order to avoid a publication bias and its negative consequences, namely faulty evaluations of therapies, flawed therapy recommendations, unpromising treatment attempts and unneeded clinical studies (Mathews et al. 2011; Müller & Christen 2011; Nuttin et al. 2014; Rabins et al. 2009; Schläpfer & Fins 2010; Woopen et al. 2012). Investigational treatments, in which a given technology is applied to new, but frequent indications, e.g., DBS for OCD, should not be allowed; rather, all new applications should be investigated in clinical trials of the appropriate size and statistical power. Fins and coauthors have recently demanded that the US Congress and federal regulators should revisit the FDA's humanitarian device exemption in DBS for OCD, and demand that it should undergo clinical investigations using an investigational device exemption.[35] They argue convincingly that the humanitarian device exemption is mis-

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[34] E.g., recent advances in functional imaging hold promise for noninvasive methods of predicting memory decline after epilepsy surgery (Hamberger & Drake 2006).

[35] A *humanitarian device exemption* (regulated in the Safe Medical Devices Act of 1990), allows a manufacturer to market a device under certain conditions without subjecting it to a clinical trial. This designation is available only for devices intended to diagnose or treat conditions that annually affect 4,000 or fewer people in the United

used for bypassing the rigors of clinical trials, since OCD is not an orphan, but a prevalent condition, and that the current market-driven regulatory strategy is detrimental to patient safety, scientific discovery and research integrity (Fins et al. 2011b).

5. Careful observation of single cases: Besides clinical studies, case studies contribute much both to clinical experience and to scientific understanding. By way of example, the knowledge of adverse effects of DBS has been spread mainly via case reports (Christen & Müller 2011). Single cases may offer new insights into physiological or pathological brain mechanisms; this is well known from lesion studies. The same is true for DBS: Important insights could be gained from reports about the effects of misplaced stimulation electrodes (e.g., Bejjani et al. 1999;[36] Bejjani et al. 2002[37]), too high stimulation parameters (e.g., Krack et al. 2001[38]) and unsuspected positive or negative side effects (e.g., remission of comorbid addiction after DBS for other mental disorders, e.g., Kuhn et al. 2007 and 2009a). The careful documentation and publication of extraordinary single cases is important for the scientific progress; first for developing new indications of a given therapy (e.g., DBS for treating addiction); second for anticipating possible adverse effects (e.g., impulsive aggressiveness after DBS); third for investigating causal mechanisms of the observed effects. This highlights the importance of case studies besides knowledge based on statistical evidence.

Furthermore, it is not sufficient to publish outcome studies which average across patients to provide a unitary measure of outcome. Since the outcome of interventions in the brain often varies extremely between patients, it is necessary to report both good and poor outcomes separately. Cross-sectional group research does not reveal the different individual trajectories and provides only limited clues about which factors are most relevant in effecting positive change for an individual. It is important to study individual outcomes, particularly by identifying subgroup patterns that can become lost in whole-group analyses. To overcome this systematical shortcoming, long-term follow-up studies of outcome, particularly of neuropsychological and sociopsychological outcome, are necessary (Wilson et al. 2005; Baxendale et al. 2012). Particularly cases with unfavorable or unexpected outcome should be investigated, since they offer extraordinary chances for scientific discovery and improving the techniques used (Fins et al. 2011b; Kubu & Ford 2012).

States. An *investigational device exemption* requires that the device be subject to a clinical trial that collects data on its safety and efficacy. This designation allows an institution to conduct an appropriately powered, hypothesis-driven clinical trial to assess the device's safety, efficiency and mechanism of action (Fins et al. 2011b).

[36] Transient acute depression occurred when stimulation was delivered to the left substantia nigra, 2 mm below the site where stimulation alleviated the signs of Parkinson's disease (Bejjani et al. 1999).

[37] A patient showed aggressive outbursts during intra-operative test stimulation (Bejjani et al. 2002). The cause of this behavior was an electrode located in the triangle of Sano between the medial STN and the posteriomedial hypothalamic region, which used to be selectively lesioned to treat medically intractable aggressive behaviors in severely affected psychiatric patients.

[38] Stimulation of an electrode in the STN with stimulation parameters 50% higher than therapeutic induced funny associations, leading to infectious laughter and hilarity in two patients (Krack et al. 2001).

6. Comprehensive investigation of adverse effects, particularly of sociopsychological sequelae: Since the risk-benefit profile of a therapeutic approach is decisive for recommending it to patients, research about adverse effects has an important role. Because of the broad spectrum of possible adverse effects, a multitude of test instruments has to be used. Whereas for the measurement of most sensory and motor deficits reliable instruments are available (although not consistently used),[39] this is not the case for the most mental, behavioral, social or economic consequences of brain interventions. Especially information about psychosocial and economic consequences of interventions in the brain is scarce. Generally there is a surprising lack of studies about these issues; and most of the existing studies have too small samples and too short follow-up times, and their focus is mainly on side effects which are easily measurable instead of those with the highest impact for patients (Müller & Christen 2011). For DBS, data records are much better than in other neurosurgical fields, but even there, these general shortcomings exist (Woopen et al. 2012). Nuttin et al. (2014) rightly demand for postoperative evaluation and long-term follow-up of all patients who underwent psychiatric neurosurgery; they plead for complete comprehensive postoperative assessments, including neurological, psychiatric and neuropsychological evaluations, and additionally recommend evaluations of the psychosocial outcome.

More research is needed to identify predictive factors for a good outcome, particularly for an outcome that is perceived as good by the patients. By way of example, the paradox of dissatisfaction has been noticed in DBS patients: In spite of a good clinical (particularly motor) outcome, many patients are not satisfied with their postsurgical situation, partly due to false expectations, partly due to preoperative (subclinical) psychiatric problems (Krug 2012; Maier et al. 2013). Not only mental disorders such as apathy and depression, but also adverse social sequelae cause dissatisfaction; e.g., problems in the family or at work due to personality alterations, sometimes with fatal consequences as divorce or unemployment. This highlights the need of investigating subjective indicators of well-being and quality of life in measuring the outcome of interventions (Müller & Christen 2011; Krug 2012; Woopen et al. 2012) and of evaluation strategies that account for the broader psychosocial context of patients (Illes 2010).

7. Development of instruments for measuring subtle mental alterations: Since personality changes are a main ethical concern and a central factor of patient's satisfaction with an intervention, instruments to evaluate even subtle changes should be developed further and complemented by qualitative and narrative methods (Krug et al. 2010; Lucius-Hoene 2008; Merkel et al. 2007, pp. 284-285; Müller O et al. 2010; Müller & Christen 2011; Witt et al. 2012;

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[39] For example, in studies about the treatment of vestibular schwannomas, the important outcome parameters hearing preservation and tumor control are not standardized; therefore the comparison of outcome studies is difficult (Müller S et al. 2010).

Woopen et al. 2012). Furthermore, changes of the socio-moral attitude and behavior following neurosurgical interventions should be documented, measured, and evaluated, since a comprehensive evaluation of the outcome of a given therapy has to consider not only the patients' wellbeing, but also possible behavioral changes which could affect third persons.[40]

8. Long-term prospective follow-up: Long-term, optimally prospective follow-up studies are necessary for guaranteeing quality. Nuttin et al. (2014) recommend that research and clinical protocols should include support for long-term safety and efficacy studies on psychiatric neurosurgery for at least 5-10 years of follow-up. Unfortunately, there is a lack of interest of providers, industry and government in paying for outcome analyses (Hahn in Lieberman et al. 2008). Here the governments are demanded to fund long-term outcome studies.

Clinical practice

1. Information for patients: For decision-making, patients need independent, evidence-based information about benefits and chances of different therapy options. As we have proposed for DBS (Müller & Christen 2011), a "living database" should be developed, ideally for all neurosurgical therapies, with open access for physicians and patients. It should contain comparative data of single centers about the morbidity, the incidence of complications and adverse effects, the neuropsychological outcome and quality of life following neurosurgery. The data should be continuously updated.

2. Inclusion and exclusion criteria: It is a challenge to establish criteria (beyond the accepted medical criteria) for selecting patients for a given intervention, since they have to be both responsible and just, i.e., they have to protect vulnerable patients, but should not exclude patients who could profit from a given intervention. Although the criteria should be formulated as general rules, they should allow individual exceptions (Müller & Christen 2011). By way of example, patients who have a psychiatric diagnosis are especially vulnerable; this speaks in favor of excluding them from DBS or epilepsy surgery. On the other hand, it would not be just to exclude them from interventions from which they might profit, perhaps extraordinarily, since the interventions could even cure the psychiatric disorder. Therefore, psychiatric diagnoses should not be considered as an absolute contraindication; rather existing or former (neuro-) psychiatric disturbances should be carefully considered, since they could be exacerbated after the intervention and might undermine its benefits (for epilepsy surgery: Foong & Flugel 2007; for DBS: Bronstein et al. 2011; Maier et al. 2013). Instead of excluding patients with certain psychiatric disorders generally, their capacity to provide informed consent should be assessed carefully (see also Glannon 2010; Laxton et al. 2013; Mathews et al. 2011).

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[40] The research group "Effects of DBS on moral agency: Developing a methodology to identify and evaluate this phenomenon" (supported by the Swiss Academy of Medical Sciences, Käthe-Zingg-Schwichtenberg-Fonds, leaded by Markus Christen) has been working on this topic. For first results, see Tanner & Christen (2013).

Particularly in case of elective interventions, the patient's expectations are another important criterion. The expectations of patients often go beyond relief of symptoms and comprise hope for general improvements in life such as more happiness, better social integration, or more independence (for epilepsy surgery: Baxendale & Thompson 1996). Unrealistic expectations can undermine clinical benefits and cause subjective negative outcomes (Krug 2012; Maier et al. 2013). To avoid the paradox of dissatisfaction, it is recommended to discuss the expectations with the patients, and in case of unrealistic expectations to reconsider the intervention with the patient. In clinical research, additionally the degree of therapeutic misconception[41] should be addressed carefully (see also Nuttin et al. 2014).

3. Pre- and post-interventional neuropsychological and psychiatric assessments: Because of the frequency of post-interventional cognitive decline and psychiatric disturbances, but also because of the chance that pre-existing neuropsychological or psychiatric conditions resolve after the intervention, pre- and post-interventional assessments should be performed generally: First, a psychiatric assessment helps physicians to identify patients at risk for postoperative psychiatric disturbances, so that patients can be excluded for whom the risks are too high, and the others can be offered treatments of existing psychiatric disorders, e.g., depression, apathy or impulse control disorders, before surgery. Second, information about the individual risk of postoperative psychiatric complications is important for patients' decision-making. Third, more intensive postoperative psychiatric or psychological care can be arranged for patients at risk in case of surgery.

4. Patient-centred, multi-disciplinary counselling and shared decision-making: These complex purposes require multidisciplinary teams, which should include neurologists, neurosurgeons, psychiatrists, neuropsychologists, psychologists, and in particularly complex cases, also bioethicists and lawyers (see also Nuttin et al. 2014). Since for many brain disorders, several therapy options are available of which none is superior in all aspects, but which have different risk-benefit-profiles, patients should be counselled comprehensively and according to evidence-based medicine about all available therapy options. Besides evidence-based medicine, it has to be taken into consideration that some patients refuse certain therapy options because of specific fears (e.g., fear of radiation) or because of moral or ideological reasons (e.g., concerns against using embryonic stem cells) (Müller S et al. 2010; Northoff 2001).

The counselling has to include also therapy options which are not offered by the institution which performs the counseling; even if the consequence is that the patient will be treated in another institution. Optimally, a multidisciplinary team assists the patients in the decision-

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[41] Subjects that hold therapeutic misconceptions about participation in a clinical study fail to recognize adequately the key differences between treatment and clinical research (Lidz et al. 2004). Patients with severe depression, who wanted to undergo DBS, showed therapeutic misconception; whereby subjects who were more depressed demonstrated fewer misconceptions (Fisher et al. 2012).

making process; if such a team does not exist locally, the patients should be referred to specialists of all relevant therapies (Müller et al. 2010). Multidisciplinary teams are also recommendable since they provide the opportunity for a difference of opinion to enter into the discourse; thus they provide a safeguard against consenting to interventions out of deference to the neurosurgeon (Ford 2009).

Candidates for brain interventions should be carefully informed about the possibility of mental changes and the intervention-specific risk of psychiatric disturbances and personality changes after the intervention. The risks and chances of psychiatric changes should be discussed with the patient and – if possible – with his family. Counseling should comprehend also the individual situation of the patients, especially their professional activity, social integration, and psychic condition. Before a decision about an intervention into the brain is made, also the patient's goals for choosing a certain therapy, his/her interpretation of quality of life and his/her attitude concerning possible handicaps and death should be considered. That means more than informed consent: Especially for treatments of the brain, *shared decision-making*[42] should become the standard.

5. Advance directives or Ulysses contracts, respectively, should be offered to the patients, particularly for those at risk of personality changes or of loss of autonomy. Patients should, if possible, consider their treatment preferences not only for the planned outcome but also for a disastrous outcome, such as permanent loss of consciousness. Advance directives and the determination of attorneys are helpful tools for preparing for the worst case. Ulysses contracts are particularly helpful for dealing with transient states of psychosis or mania following surgery, DBS, or drug therapy.

6. Postoperative psychiatric and psychosocial care: Since neurosurgical patients often need much time to adapt to possible personality changes and other side effects, it is important that satisfactory arrangements are in place for the postoperative management (Sakas et al. 2007). This holds particularly for patients who undergo epilepsy surgery or DBS, since they are at risk to develop psychosocial maladaptation in spite of a good clinical outcome ('burden of normality syndrome'; Gilbert 2012; Wilson et al. 2001).

7. Outcome analyzes: Clinics should follow each of their patients long enough to evaluate the success or failure, respectively, and possible long-term sequelae. Outcome analyzes help to prevent the repetition of former failures and to establish a good practice (Lieberman et al. 2008; Nuttin et al. 2014).

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[42] For shared decision-making see e.g., Loh et al. (2007) and Scheibler (2004).

8. Summary

This work investigates personality changes and alterations of the capability for autonomy following neurosurgical or other physical interventions in the brain from a neuroethical point of view: The ethical analysis is based on a neurophilosophical model which describes persons not as monolithic entities, but as dynamic biological systems composed of different modules that act on different levels of functional and representative complexity and have certain abilities of self-representation and self-regulation. Only in a neurophilosophical framework, interventions in the brain raise specific ethical questions, since only here they are understood as potential interventions in the core properties and capabilities of persons.

The ethically decisive question is not whether interventions in the brain can alter the personality or not, but whether they will do so in a good or bad way and whether the resulting effects on the personality are good or bad. The evaluation of iatrogenic changes in personality is a normative, not an empirical issue. Since not only interventions in the brain, but also brain diseases can cause problematic personality changes, also the waiving of indicated interventions can be ethically problematic, particularly, if they could prevent problematic personality changes or the loss of the capability for autonomy. Therefore, the bioethical principle of respect for the patient’s autonomy should not be understood only negatively in terms of respecting the patient’s therapy decisions, but also positively in terms of providing therapies which can save or restore the neurological prerequisites of the capability for autonomy.

In the introduction, the specific ethical issues of interventions in the brain which could alter the personality and/or the capability for autonomy are outlined. An overview summarizes the broad spectrum of negative and positive personality changes which can occur after different kinds of neurosurgical interventions, particularly tumor treatments, epilepsy surgery, deep brain stimulation for neurological or psychiatric disorders, and psychiatric neurosurgery.

The following chapters investigate different treatment options (magnetic fluid hyperthermia therapy, microsurgery, radiosurgery, radiation therapy, deep brain stimulation) for different brain diseases (malignant brain tumors, vestibular schwannomas, Parkinsonian disease, psychiatric disorders) ethically, particularly with regard to their impact on the patient’s personality and capability for autonomy. Thereafter, the principle of respect for the patient’s autonomy is reconsidered on grounds of the neurophilosophical debate on free will; two paradigmatic cases, namely body integrity identity disorder (BIID) and deep brain stimulation, are analysed.

In the final discussion, central issues of the former chapters are scrutinized:

1. Adequacy of Beauchamp and Childress' principle-based ethics for evaluating neurosurgical interventions: This ethical approach is prima facie adequate for ethically evaluating interventions in the brain, but at least its standard interpretation is too narrow to deal with specific ethical problems of interventions which could alter the personality and/or the capability for autonomy, particularly, if the interventions make the patients more dangerous for third persons. For the ethical evaluation of therapies with might cause personality changes, an ethical valuation of personality changes is required, since neither the conservative general condemnation of technically caused personality changes nor a libertarian abstinence in valuating personality is helpful for medical ethics. The ethical evaluation of personalities clearly outreaches any ethics on the level of medium principles. Furthermore, Beauchamp and Childress' concept of autonomy is too narrow; particularly with regard to brain disorders and interventions in the brain, the dependency of the capability for autonomy of brain functions has to play a central role. This underlines the importance of understanding respect of autonomy also as the positive obligation to save, restore or enhance the capability for autonomy if necessary.

2. The concept of personal identity with regard to personality changes through brain interventions: Although personality changes occur in a significant fraction of neurosurgical patients, and although they are a main concern with regard to interventions in the brain, the transfer of the concepts of "loss of personal identity" from the Analytic philosophy is misleading. The application of psychological continuity theories of personal identity and particularly of Parfit's theory, on iatrogenic personality changes is misleading for theoretical, ethical and legal reasons. If these theories would be taken serious by legal theorists, the most problematic consequence would be the denial of (psychiatric) advance directives; this would severely harm the patients' autonomy and eventually their mental health and social status.

Finally, general ethical recommendations (i.e. neither disorder-specific nor therapy-specific) for research and clinical praxis of neurosurgery are derived from this investigation, particularly with regard to the potential of changing the patients' personalities and capabilities for autonomy.

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Internet resources

www.magforce.de/fileadmin/magforce/3_studien/Update_patient_information/Questions_and_Answers.pdf (MagForce) (assessed: 06.02.2014) www.medtronicdbs.com/parkinsons/about/benefits-and-safety/index.htm (Medtronic) (accessed: 07.02.2014)

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
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12.03.2014 ....

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