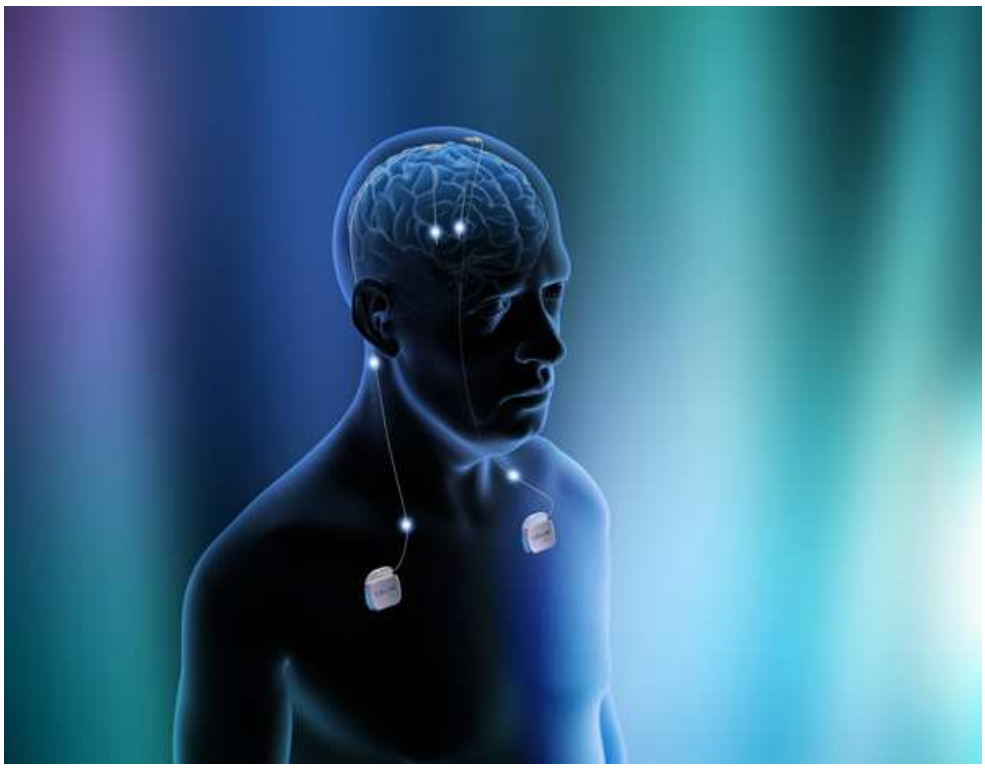
Assessing the Plausibility of the Expectations about Deep Brain Stimulation as Treatment for Depression



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Content

1. Introduction

Benabid, a neurosurgeon involved in the development of Deep Brain Stimulation (DBS) for Parkinson's Disease is one researcher who has suggested that this technology could be advantageous for the treatment of Parkinson's as well as other disorders (Benabid 2003). This suggestion is a result of discussions surrounding the treatment of patients with mental disorders such as depression. The idea of DBS as a treatment for mental disorders has been taken up by the Defense Advanced Research Projects Agency (DARPA). In 2013 DARPA announced that they would conduct a study, launching a five year program in which they plan to invest more than 70 million dollar to perform research using DBS (Rukovest 2013). This announcement from DARPA is the starting point for this thesis. The DARPA project manager Sanchez claims that "there is still a great burden of psychiatric and neurologic diseases that remain unaddressed" (o.c., p. 15), and that the project will develop novel brain interventions to address these disorders. There is a particular interest in treating soldiers and veterans since many develop different neuropsychiatric disorders such as depression, anxiety, and posttraumatic stress disorder (o.c.). DARPA's aim is to have a DBS prototype to treat these different mental disorders within five years. (Tucker 2014). Rukovets (2013) quotes the Director of Research, Grafman, who explains that the goal behind the investment of DARPA and the research of DBS as a treatment for mental disorders is to combine an analysis of all DBS treatment possibilities with research to improve the current knowledge. This is the understanding of brain networks and electric signal patterns (o.c.). Grafman thinks that "there may be a role for an artificial implant of some kind that you can turn on and off, like DBS for Parkinson's in the neuropsychiatric domain" (o.c., p. 15).

DARPA sees DBS as a treatment and also as an opportunity to interact with the 'healthy' brain by electronic device implantation. Sanchez mentions that the hope is that these interactions will help to identify brain networks involved in different mental processes, such as memory and cognition (Talan 2014). To reach this goal and acquire insights about mental disorders, DARPA will monitor different brain regions before direct stimulation (Hsu 2014). To create their prototype, DARPA will use DBS to detect and categorize emotional reactions in the amygdale. The idea is that strong emotional reactions can be avoided if the activation of the amygdale is tempered. Liao (2014) has suggested that when the strength of emotional memories is reduced, they will not turn into strong long-term memories. This might help to reduce potential trauma after military service. Talan (2014) argues that after DBS treatment in epileptic patients, the patients performed better playing a computer game when the electrodes were used to stimulate the entorhinal cortex. Sanchez believes that DARPA can "revolutionize treatment for all types of brain problems" (o.c., p. 8).

Overall, DARPA will investigate DBS as a possible technology for targeted stimulation of certain brain areas to be used as a treatment for mental disorders, and to restore normal brain functions (Hsu 2014; Tucker 2014). This case shows that there is currently an increasing interest in new usages

for DBS in the military sector, especially to treat the mental disorders discussed previously. This new interest results in several expectations about DBS. The status of current development and research of DBS as a treatment for patients with depression and the rising expectations with this treatment are investigated in this thesis. To investigate how we could assess the desirability of DBS for depression, I will analyze the plausibility of the expectations about DBS as a treatment for patients with depression. An approach to investigate the plausibility should overcome the problem that ethical research works alongside the speculations of new technological possibilities. Thus, I will not evaluate the desirability of this treatment, but investigate whether the expectations that it might become a desirable technology are plausible or not. This first chapter introduces the main topics of this thesis, the research question, and the outline of this thesis.

1.1 Experimental Phase of DBS for Depression

One of the first basic medical experiments with DBS as a possible treatment for depression, performed by the research group of Mayberg, concluded that DBS represents an efficacious novel intervention for severely disabled patients with treatment-resistant depression (Mayberg, Lozano et al. 2005, p. 657). Four out of six patients achieved sustainable clinical response after six months DBS (o.c., p. 656-657). The results could be seen as striking, but further research seems necessary with larger patient groups in order to investigate the first response to the treatment, as well as the long-term and recurrent effects of depression (Schlaefer and Lieb 2005). The group of Mayberg is one which studies DBS as a treatment for depression, but other research groups also investigate this treatment, such as Jimenez et al. (2005) and Schlaepfer et al. (2013). Galvez et al. (2015) is critical towards all research. After reviewing ten experiments with DBS for depression, they argue that there are many uncertainties around DBS and its treatment possibilities, especially considering long-term effects. In their view, to know whether or not this technology is superior to medical treatments in cases where depression is unresponsive to drug or other therapies, more (long-term) medical experiments are required (o.c.). I give a more extensive analysis of different studies in chapter four. I will elucidate on some expectations throughout this thesis (appendix A shows an overview of some expectations).

1.2 Deep Brain Stimulation in Ethical Debates

The technology of DBS and the publication of experiments outlining new applications for its use caught my attention. I was especially interested in the case put forward to use DBS as a treatment for depression, alongside the research DARPA has proposed. At the moment DBS is already accepted as a treatment for Parkinson's Disease and Obsessive Compulsive Disorder, but the treatment of depression with DBS is still in its experimental phase. Ethicists are mainly involved with the overall ethical implications of DBS as a treatment. However, the ethical issues that are important when DBS

may be used as treatment for depression might slightly differ from ethical issues considered in the treatment of Parkinson's Disease. For example Glannon (2009) considers personality changes as a possible side effect of DBS treatments. This change in personality is not necessarily unwanted or undesirable, and maybe even inapplicable in the treatment of patients with mental disorders such as depression (Pacholczyk 2011). Chapter six will focus in more detail on personality change and other possible ethical implications. Although it can be important to consider ethical issues in early stages of development, when considering speculations, we can end up with hopes but do not know exactly the actions and results of this treatment. I explain this in the following paragraphs.

1.3 Expectations Resulting in Speculative Ethics

The rise of expectations, about DBS becoming a treatment for depression, considering clinical experiments, DARPA's plans, and media attention that surrounds it, is a common phenomenon in innovation processes. As sociologists studying innovation have pointed out, new technologies and coming changes first pre-exist only in the imagination, in expectations, and visions which shape their potential (Borup, Brown et al. 2006, p. 285). According to the Merriam-Webster dictionary, an expectation is (1) "a belief that something will happen or is likely to happen" and (2) a "feeling or belief about how successful, good, etc., someone or something will be." This definition already shows us that an expectation consists of two different parts, a predictive, more factual aspect and a normative element. Borup et al. (2006, p. 268) discuss that expectations can be seen as fundamentally generative in guiding activities, providing structure and legitimation, attracting interests, and fostering investment. Expectations can have an influence on the scientific and technological change, will define roles, clarify duties, and offer a shape of what to expect and how to prepare for opportunities and risks (o.c., p. 268). Rusconi and Mitchener-Nissen (2014, p. 2) listed benefits for research and development:

- To guide and drive research activities and to enhance interactions and communication.
- To justify and legitimize the mobilization and allocation of resources of future benefits.
- To attract the attention and engagement of actors and collaborators.
- The production of experiments, models, research projects, and calculation will be enabled.
- Construction of future scenarios and formation of a consensus to counterbalance the uncertainties of a new technology.
- Enlisting public support through presentations of futures.

Besides the benefits of expectations, there is a downside. Van Lente et al. (2013, p. 1615) argue that waves of media attention for a certain technology under development can raise high expectations about its possibilities, a 'hype'. For example, expectations that foresee a bright future but which create overly-positive expectations can ultimately damage credibility and reputations (o.c., p. 1615). It is a tempting way to characterize technological development, but hypes are usually followed by disappointment when the high expectations are not met (o.c., p. 1616). However, as Swierstra and Rip (2007) discuss, speculations are not only caused by media attention. Some expectations are a reflection of the promises raised by the researchers to attract attention for financial, political, and

moral support. Unrealistic expectations are inevitably unmet according to Rusconi and Mitchner-Nissen (2014, p. 4), and drawbacks can include:

- Unrealistic hype that detracts from the long-term value of the basic science.
- Financial losses and difficulty in securing sources in fields which have suffered from a collapse of expectations.
- Resources being diverted from more realistic, less exciting, research.
- Undermined trust that can slow or prevent future progress in the research.
- Reputation of individuals, companies, institutions, or research fields can suffer as promises fail to materialize in the present.
- Different people can suffer as a result, for example individuals who suffer financial loss from investing, or patients who suffer emotionally having believed the claims to treat their condition.

1.3.1 Expectations about DBS for Depression

As described above, DBS for depression has been used by several research groups. Although the number of experiments performed is limited and many uncertainties abound, a variety of expectations about DBS as a treatment for depression are circulating. Strickland (2014) imagines a world free of disability, depression, and loss of memory. He expects the use of DBS as a therapy to treat patients with depression, but also used for those who do not yet suffer from any disease. Biological or pharmacological therapies will be discarded in favor of electronic additions to human bodies (o.c.). Sanchez expects that "the neurotechnologies we will work to develop … could give new tools to the medical community to treat patients who do not respond to other therapies, and new knowledge to the neuroscience community to expand the understanding of brain function" (Engelking 2014, p. 2). The investment of DARPA to investigate DBS as a treatment for mental disorders will focus on military personnel at first, but also underlines its potential to benefit everyone (o.c., p. 2). Although Sanchez sees DBS as "a transformative approach to interact with the brain", he acknowledges that it could take many years before individuals would benefit (o.c., p. 8-9). Talan (2014) points out that the DARPA project stems from the idea that successes for DBS as a treatment for depression are proven. Current evidence is limited, however, it is hard to assess how seriously one should take the high expectations cited above, in particular for relative outsiders. This poses a problem not only for the general public and policy makers, but also for ethical reflections on DBS for depression. The beliefs of DARPA are that the advances made in DBS to successfully use stimulation to treat severe depression suggest that the technology could be developed further (Talan 2014).

The military domain and the medical domain are involved in experiments with DBS for depression. Fisher (2013) suggests that psychiatrists want to use DBS for the treatment of psychiatric disorders. He discusses that DBS is currently used to treat depression, dementia, Obsessive Compulsive Disorder, substance abuse, and obesity, and that more possible uses are beginning to follow (o.c.). "Unintended side effects have also spurred new uses of this poorly understood technology" (o.c., p. 1). Bell et al. (2010) argue that patient's hopes and expectations of DBS may

have been raised to unrealistic levels by enthusiastic media reports, such as the article of Fisher (2013). Another example of a very optimistic expectation is argued by Solomon (2014) during a TED radio talk where he says that "the most radical breakthrough is Deep Brain Stimulation (…) absolutely astonishing results with people who failed every other treatment." This statement suggests that DBS will be a desirable treatment for patients who have not benefitted from other treatments.

These previously discussed expectations are visible in the public domain, but there are expectations in the academic domain as well. Koivuniemi and Otto (2014) argue that researchers and physicians expectations are not always reliable. Researchers and physicians can have intuitions that may become clouded by the discovery of each effect. Take for example Lozano and Mayberg (2015) discussing that DBS should offer a lifeline to people who might otherwise be doomed to endless despair. This argument tells that it is beneficial for some patients, and that the technology should become an accepted treatment. In contrast, some studies present DBS for depression with a bit care, for example "DBS might be a safe and efficacious alternative method" (Schlaepfer, Bewernick et al. 2013, p. 8). Although this is still a positive expectation of DBS as a treatment for patients with depression, it is expressed with less certainty. Besides all arguments that might create expectations in regards to the possibility of DBS, Moss (2013) suggests that it may become an actual treatment option, stating that "DBS is emerging as a viable option for treatment-resistant depression." She discusses that after six months, results show significant improvements in patients with depression, with a lasting response unless the battery runs out. Overall, expectations can range from the unrealistic, promising a new switch in the brain, towards which could be reported as an alarming expectation. All drawn images and stories from the scientific and public domain can easily result in high interest, in both uncertain and possible false expectations.

1.3.2 Anticipatory or Speculative Ethics?

Shilton (2015) says that we can use the design phase to reflect on the impact, use, and potential consequences of a new technology. Anticipatory ethics seeks to highlight the ethical challenges in emerging technologies, and encourages actors to discuss ethics during the design process. Brey (2012) suggests that we incorporate anticipatory ethics in the design of new technologies. Ethical issues in the research and development stage cannot be reliably known as we cannot know the future (o.c., pp. 1-2). It is difficult at the moment to know which ethical issues will play out when the treatment of DBS for depression is utilized. As Brey (2012) discusses, it seems important to anticipate ethical issues in the early stages of research and development, however, it is difficult to know the future.

Nordmann (2007) was the first to point out the risk of anticipatory ethics and the disproportionate attention of ethics towards highly speculative scenarios. In particular, he has difficulty with a concept he calls the 'if-and-then syndrome'. An if-and-then statement suggests that

when a certain technology is designed that the development will continue no matter what, and asks us to consider the potential consequences of this development (o.c.). He uses examples of human enhancement to illustrate, stating "if it should be possible to create a direct interface between brains and machines, this research threatens an invasion of privacy when machines are used to read human minds" (o.c., p. 33). These arguments show how speculative ethics invite a mandate for action, it does not matter how plausible it is that research succeeds (o.c., p. 33). Nordmann and Rip (2009, p. 273) argues how the hypothetical gets displayed by a supposed actual in if-and-then statements, the imagined future overwhelms the present. A future that was a speculative possibility is turned into something inevitable. The effect of the if and then-construction is that consequences of a development are presented as calling for ethical attention.

The exploration of ethical issues relating to emerging technologies can lead to discussions about misguided and irrelevant implications (Brey 2012). This exploration can be seen as unwanted. Therefore it is important for ethicists to know which developments require attention because as Nordmann (2007) argues, ideas of incredible futures can distract developers from ongoing design, because the if-and-then statements are incomprehensible for systematic reasoning. Discussions concerning overly 'futuristic' ethical issues are unwanted, but we need to anticipate and prepare us for unforeseen futures as well. Speculations about future scenarios can result in expectations about the use and performance of an emerging technology. King et al. (2011) argues that the major problem is the understanding of an emerging technology. Not only the accuracy of expectations, promises, and concerns are low, but also the accuracy of predicted technological development. This has consequences for the connection between ethics and technology (o.c.). An ethicist should become able to distinguish between outright speculations and 'realistic' expectations of new and emerging technologies.

1.3.3 Ethics and DBS for Depression

I showed that speculative ethics can become a problem for the assessment of emerging technologies, and that the current discourse about DBS for depression is characterized by a lot of expectations and uncertainties. As a result, ethical reflection on DBS for depression might indeed fall into the trap of speculative ethics. Looking at the existing ethical literature, can we observe such speculative ethics? Schermer (2013) argues on all possible DBS treatments, and expects that DBS will become a treatment for many mental issues, including depression. She claims, for example, that "it might even turn out to be possible to use it to enhance cognitive function, mood, or other mental functions" (o.c., p. 436). She states that cognitive enhancement will possibly fall within the boundaries of medicine, well-being, quality of life, or could fulfil 'vital' goals, claiming that "the goals of medicine do not function as a static set of aims and limits" (o.c., p. 444). Kuhn et al. (2009, p. S140) argues that "it has to be assumed that the indications for DBS and frequency of its therapeutic application in psychiatry

will increase substantially." With this assumption that ethical claims such as informed consent have to be taken into account (o.c.).

Despite the ethicists who discuss DBS as a treatment in general or for mental disorders, there are less who discuss DBS treatment for depression specifically. Johansson (2010) discusses that use of DBS should be extended and that its use for the treatment of depression is evaluated. There are gaps that need to be fully researched (o.c., p, 41). Johansson et al. (2011) discuss the possibilities of personality change when a depressive patient is treated with DBS. "A successful outcome of DBS could be viewed as a form of liberation since a hindrance for the patient to be and live authentic is eliminated when the depression is vanquished or significantly reduced" (o.c., p. 2). Although they assume that it will become a treatment, they argue that the treatment is not yet fully developed. This shows that the ethical issues are at some extent based on speculations. I will use an assessment to analyze which ethical implications might become pressing issues in the case of DBS for depression.

1.3.4 Assessing the Plausibility of Expectations

In the wake of the discussion about speculative ethics, we should not avoid all early ethical reflection entirely, but need to understand that reflections on DBS for depression could result in speculative ethics. Methods have been developed to reduce the risk of going along with unrealistic expectations. Considering this evidence, the aim of my thesis is not to assess the desirability of DBS being used as treatment of patients with depression, but to come up with an agenda for ethical debate on desirability that focuses on issues that are both plausible and urgent. To do so, I will use an approach to assess the plausibility of expectations developed by Lucivero et al. (2011). They claim that to assess the quality of expectations of emerging technologies both skepticism and imagination is necessary. Taken from Nordmann, the quality of expectations should not be taken for granted in ethics. An ethicist should avoid the unwarranted and strategic claims when building his analysis. This can be done by focusing on a specific technology instead of a general technological field and by a 'reality check' of taken for granted scenarios of technological and societal trends (o.c., p. 131). Expectations are future oriented abstractions and the rhetorical character of expectations might not limit, but provide a starting point. Even though the truth of expectations can only be considered in hindsight, the plausibility of expectations can be explored (o.c., p. 132).

Lucivero et al. (2011, p. 133) consider three dimensions in expectations; technological feasibility, social usability, and desirability. First, in regards to technological feasibility, there are different reasons why an ethicist should distrust the claims of scientific experts. As shown in history, many claims never materialize and these claims are often strategic, as pointed out by a sociology of expectations. The aim of the actor and the audience to whom the expectation is presented are important factors when analyzing the plausibility of expectations (o.c., p. 133). Controversies and

compromises take place before the laboratory presents the scientific results to the world. The arguments to convince the researchers are different from the arguments necessary to reach the broader public. The ethicist can come across these controversies and uncertainties by literature study and research on the laboratory floor (o.c., p. 133-134). Chapter four consists of the technological feasibility analysis of this thesis.

Secondly, social usability is included in order to discuss whether possible technological expectations might imply social conditions that are impossible (o.c., p. 135). For example, the visions of the use of a technology in future medical practice are built on presuppositions about this practice. Presupposition can be implausible, even if the technology itself would be feasible. Therefore, relevant current practices and the envisioned new practice have to be investigated, to create a detailed image of how the use beyond the laboratory might look like. Actors who are involved in practices of a new device can share current experiences, opinions and ideas about possible aspects that need to change, prevent expected use, or encourage use in other practices (o.c., p. 135). A useful tool is a "thick description" of the current and probable future use of the technology, pointing to the social conditions that are implicit in the expectations and helps to imagine the new technology in the social context (o.c., p. 135). The current and envisioned practices are analyzed in chapter five.

Thirdly, the desirability focusses on how the impact of a new technology will be normatively evaluated (o.c., p. 136). Although most expectations about emerging technologies suggest otherwise, often there is no unanimous understanding of the impacts that a technology will bring. Lucivero et al. (2011, p. 136) state that "the reason why engineers consider the technology 'good' might not match with doctors' and patients' considerations: whereas engineers might be considered about the accuracy of the test, doctors might be more focused on their possibilities to control the results of the test, while patients might emphasize the portability of the device." To assess how likely it is that future users and actors will accept a new technology and consider it desirable, it is important to keep in view all the different aspects and values that may come into play (o.c., p. 136). I will not analyze the desirability, but the plausibility that implications might influence the desirability.

To complicate matters, it is hard to anticipate how actors will evaluate values, since even the values they hold may change as a result of the innovation. Technology, society, and morality are bound up together and when there is a change in one, the others are invited to change, resulting in 'techno-moral change'. The ethicist can make actors more aware of the possibility of moral change by building on techno-moral changes that have occurred in the past (o.c., p. 137-138). An ethicist has to make actors aware of the possible moral changes and thereby encourage their imagination. Stimulating imagination is to reflect how the technology might change the values of actors and how these changing values might affect the acceptance. This thesis will only focus on the values discussed in literature and during interviews with all different actors, analyzed in chapter six. In view of time, the thesis does not include techno-moral changes.

1.4 Research in this Thesis

Although DBS has already been introduced within the health care system, DBS for depression is a possible emerging technology. The risk of speculative ethics is apparent when an ethical assessment of this treatment under development is performed. The goal of this thesis is to analyze how to assess the desirability of DBS for depression and avoid speculative ethics. I will perform preliminary work to prepare an assessment of the desirability of DBS for depression. An assessment to investigate the plausibility of the expectations about DBS as treatment for depression will be used to answer the research question. *"How to assess the desirability of current expectations about Deep Brain Stimulation as an emerging treatment for depression while avoiding speculative ethics?"*

1.4.1 Materials and Method

In order to reach the goal of this thesis and become able to answer the research question I distinguish plausible from implausible expectations with the use of the assessment developed by Lucivero et al. (2011). The status of current development and research of DBS as a treatment for patients with depression and the rising expectations with this treatment are investigated, with the use of literature and an empirical study, to assess the plausibility. Secondly, I evaluate how we should assess the desirability of DBS for depression on the basis of plausible expectations. Thirdly, the assessment is used to develop a critical ethical agenda for the evaluation of DBS for depression.

This study consists of a literature study and an empirical part including several interviews with probable involved actors with DBS for depression. I used the literature study to present the current treatment of depression and development status of DBS for depression. This literature used to analyze the current situation and the possible expectations about the future or the use of DBS in the clinical settings of the care of depression. In ability to distinguish between plausible and implausible expectations raised in literature I used the empirical part. Several aspects taken from literature were questioned during several semi-structured interviews. In chapter two I describe the current diagnostic and therapeutic procedure for patients with depression. Physicians for example were questioned about this procedure in the actual clinical settings. The different experiments with DBS for depression are described in chapter four, and this analysis from literature was used to form questions about the experiments with this technology and developments.

Overall, information from current practice, experimental settings, and possible development was used to question the technology and the possibility to embed DBS in the psychiatric care. The answers to questions considering desirability and possible ethical implications were used as a starting point and compared with ethical literature considering DBS in general and specific for depression. For example, the arguments of interviewees about possible personality change were compared with the

arguments in literature. An overview of the questions is given in appendix B. I have updated the questions before each interview with the use of information about the background of the interviewee, and with the use of knowledge obtained by previous interviews.

The empirical part is used to analyze the technological feasibility, social usability, and desirability of DBS as proposed in the assessment developed by Lucivero et al. (2011). I have performed several interviews which can be divided in four groups. First, different professionals involved in research of DBS as a treatment for depression were interviewed, such as researchers, physicians, and development companies. The questions were based on current literature and presented results of clinical trials. Problems in the technological domain as well as the medical domain and society are questioned. More specific information about the technological aspects that underlie DBS for depression was obtained by an interview with a company that develops the devices.

Secondly, different physicians who are not involved with the research on DBS as a treatment for depression were included. Questions considering the technology were asked to these actors as well, but the focus is on the social and desirability aspects of this technology in clinical practice. Thirdly, two interviews with insurance companies were used to investigate the probability of incorporating DBS in current psychiatric care. Fourthly, one patient was questioned. The questions asked to this patient were mainly used to analyze the desirability. It is very hard to find patients who are willing to be interviewed. Therefore, due to this, only one patient was questioned and more information about experiences of patients within psychiatric care was obtained from experience stories.

To analyze how we should assess the desirability while avoiding speculative ethics, the expectations raised in literature are compared with the results from the interviews. Quotes of the arguments raised during the interviews were used for chapters four, five, and six to underline discussions. Most quotes were obtained from frequently repeated arguments by different actors. In some cases, interesting or controversial quotes were used as well to show a different view in the discussion.

1.4.2 Outline of the Thesis

This thesis consists of seven chapters. Chapters two and three frame the topic of this thesis, depression and the assessment of expectations. These chapters are based on literature and consist the motivation behind this thesis, the underlying concepts of depression, and the methodology of technology assessment for emerging technologies. I start in chapter two with an historical overview of depression to show different views of this disorder and how we classify it nowadays. Following, a description of the diagnostic procedure, the treatment protocol, and all possible treatment options for depression. The historical overview and description of the psychiatric care of depression are necessary to understand the possible position of DBS in the treatment protocol and the evolving ideas of different actors about

(care of) depression. Chapter three elaborates on the assessment method developed by Lucivero et al. (2011) as I used this approach to assess the plausibility of expectations.

The following three chapters are according to the three dimensions of the assessment of expectations and include information obtained from literature as well as from the empirical research part of this thesis. The assessment as proposed by Lucivero et al. (2011) used to discuss the technological feasibility (chapter four), social usability (chapter five), and desirability (chapter six) of DBS in the treatment of depression. As described previously, the different aspects of the assessment are investigated with the use of literature research and empirical research. I compare research and expectations raised in literature with the view of actors included in the interviews in chapter four and five. I start in chapter four with the experiments performed with DBS for depression and the status of possible further development of the technology. This was as well the start for the interviews and the arguments of interviewees are compared with the literature on the experiments and possible development.

The concept of script is introduced in chapter five, followed by a script analysis of the current treatment process of depression based on literature and the empirical part about the current care of depression. Different scenarios based on the possible embedding of DBS in the psychiatric domain follow. These scenarios for the embedding of DBS for depression are based on the experimental settings and the view of different actors included in the interviews. I discuss the desirability in chapter six, establishing the issues raised and discussed during the interviews. The discussion points during the interviews were compared with ethical literature considering DBS as a treatment in general and specific as treatment for depression. I end this thesis with an overall conclusion and reflection. The reflection includes an evaluation on the approach used, the empirical part of this thesis, and possible views on conflicts or obstacles for the embedding of DBS as treatment for depression.

2. Depression

Depression is currently being treated as a disease and sufferers of depression are being incorporated within the health care system as patients, but that has not always been the case. The past and current perspectives are taken into account in this chapter to evaluate the differences in time. High-tech ideas to treat mental disorders like depression are being introduced step by step into the minds of society. However, these experimental technologies require further investigation and evaluation before we should discuss the desirability. Depression is a mental disorder belonging to the psychiatric domain and medical expertise of psychiatrists (Perring 2010). This mental disorder includes a variety of possible symptoms and its definition has changed over time. The disorder of depression is discussed in the following paragraphs, starting with the historical perspectives and classifications (or categories) of depression. This sets the basis of this thesis and formulate answers to questions like 'What is depression?' and 'Why Deep Brain Stimulation can be used as a treatment for depression?' Different speculations about the causes and theories behind depression are given in section 2.1. In section 2.2 the diagnostics and different treatment methods for depression, including non-neurostimulating as well as neurostimulating therapies, are thoroughly described. The explanation of depression and its possible treatments functions as a base for a better understanding of the current progress within the medical field and the treatment of patients with depression. This basis can be used for example in the fifth chapter to analyze the script of DBS for depression.

2.1 Perspectives throughout the History of Depression

The understanding of psychiatric disorders like depression has been subject to numerous changes over time. I start at the roots of psychiatry in the Ancient Greek philosophy (Glas 1992, p. 25) and continue the overview towards the current perspectives. This overview gives an understanding of the developing knowledge about the disorder we now call depression. It can assist for example to evaluate the desirability of different actors for a specific treatment, in this thesis DBS. The historical perspective also shows why we consider it as a disorder, why we define patients, and search for the best care possibilities for these patients. DBS might be an additional factor to the best care or not.

2.1.1. Melancholia in Ancient Greece

Although it was not originally named "depression", there has been a certain level of understanding for this mental disorder. There seem to be a lot of important Homeric heroes in Greek history who have reportedly suffered from melancholia (o.c., p. 25). As Glas (1992) argues, there is a consensus noticed in these stories. According to Greek philosophy, the cause of melancholia can be found in the direct surroundings of a hero, or is attributed to evil demon possession. The view that melancholia was caused by demons was rejected in the time of Hippocrates (Kusters 2013). Observation, reason/logic,

and the study of basic principles which cause depression, or as the Greeks still call it “melancholia”, became established practice (Glas 2003, p. 3).

Another possible explanation behind the change of mental states was sought in the equilibriums of the four bodily fluids (Kusters 2013). This speculation was called the Corpus Hippocraticum and includes the theory of four bodily fluids, called humors: blood, yellow bile, black bile, and phlegm. This humors theory was a modification on the work of Empedocles, who argued that the world was a mixture of four elements: earth, fire, air, and water (Glas 2003, p. 3). Glas (1992, p. 26; 2003, p. 3) explains that each humor is related to a season and a set of primary qualities. The fluid will increase in that particular season, with its associated qualities. Blood is related to spring, heat and wetness, yellow bile is related to summer, heat and dryness, black bile is related to winter, dryness and cold, and phlegm with fall, cold and wetness. Thus, according to this theory on humors, melancholia was an increase of black bile (Glas 1992, p. 27). The physicians defined the causes of melancholia as an increase of black bile that they believed caused emotional and behavioral changes (o.c., p. 27).

2.1.2. Middle Ages and Renaissance

In time, the stance towards melancholic individuals has been changed. The humors theory was still in use in the middle ages, but there were two different views for melancholia. It could be, for example, an excess of natural black bile as well as an excess of unnatural black bile. Beek (1974, p. 98) discusses that an increased amount of natural black bile, the thick and sediment-like melancholic humor, causes a red flush of the head and a feeling of a heavy head. The person will have a bitter-sweet taste, the taste of natural black bile, a weak pulse, and the urine will be red and thick. When a patient suffers from excess of unnatural black bile, he will become agitated about funerals and will hold the belief that he will die soon. The pulse will become higher due to unnatural black bile and the urine is thin and lead-colored (o.c.).

Melancholia was also associated with a longing for change of the environment caused by a sort of listlessness and restless boredom (Glas 2003, p. 7). The anthropologic dimension of melancholia was an agitation of the human kind that was caused by the passion of humans to enter a new era (Glas 1992, p. 30). Besides the increase noted in self-awareness in the Middle Ages, the “Renaissance” period introduces connections between astrology and disease occurrence (o.c., p. 28). Saturn was introduced in the case of melancholia and according to this belief, people who are born under the influence of Saturn or people who have a constellation on Saturn are more susceptible to melancholia. They are expected to live on the edge of tragedy. These examples show that scientists or physicians in the Middle Ages and Renaissance period tried to form a connection between symptoms and disorders, or between a misbalance and symptoms (o.c.).

2.1.3. Modern Ages, the Time of Confinement

The beginning of the modern ages was a time of confinement for the mental ill individuals (Foucault 1972, p. 55). Glas (2003, p. 13) explains that melancholic persons were perceived as delusional or sufferers from a delirium without fever. Additional symptoms were fear, restlessness, insomnia, weariness, and discomfort in many different parts of the body. In the 19th century, medicine was aimed towards a more neurocentric orientation with a strong focus on sensitivity and cognitive capabilities. Neurologists were introduced to the treatment of mental disorders in the 20th century. They have reportedly advised many different therapies, ranging from taking rest or insulin therapy to having lobotomy or electroshock therapy (Kusters 2013).

Apart from the changes in treatment approaches, the first classifications of mental disorders start to take place. Judgments were based upon the classifications of mental disorders which ranged from partial insanity to complete disability. Melancholia for example, was considered as a disorder of the partial insanity spectrum (Glas 2003, p. 13). Kraepelin was the first who had set the borders for depression in 1920. He called for research on physical causes that could underlie mental disorders (Glas 1992, p. 31-32). The classification was an attempt to make diagnosis of mental disorders more reliable with observations that must be supplemented by examination (Double 2002, p. 903). His work was based on natural scientific concepts and the connection between pathogenesis and manifestation, which are both important for modern psychiatry and the understanding of mental disorders (Ebert and Bär 2010). After Kreapelin's classification, depression became a separate part of psychiatry (Glas 1992, p. 31-32).

A couple of years later, in 1952, a method for the classification of mental disorders was created and documented. The Diagnostic and Statistical Manual of Mental Disorders I (DSM) represented a fundamental change in the conception and treatment of mental disorders. More individuals than ever before were seen as mentally ill due to this DSM I and thus more people would benefit from therapy (Ramirez 2014). The number of diagnostic categories increased over time from 106 in DSM I to 357 in DSM IV, which was created in 1994 (Double 2002, p. 902). The DSM is still considered a very important tool for the current view and diagnosis of depression. The definition of depression according to the DSM is described in the Diagnosis section.

2.1.4. Depression in the Current Health Care System

The previous paragraphs have shown that from the times of ancient Greece or even before and towards modern ages, not only the name, but also the conception and understanding of depression changed. This change had started with a search for (physical) explanations for people who were perceived as 'different'. The criteria of diagnosing sufferers from depression had changed over time, possibly because of the difficulty to elucidate the pathophysiology of depression due to the heterogeneity of

this disease (Hasler 2010). One hypothesis argued by Hasler (2010), is that a depletion of the neurotransmitters serotonin, norepinephrine, or dopamine in the central nervous system is a pathophysiological basis for depression. Serotonin is currently the most extensively studied neurotransmitter (Neumeister, Konstantinidis et al. 2002). The dysfunction of the central noradrenergic system is based on evidence of decreased norepinephrine metabolism, and the reduction of dopamine neurotransmission was consistent with a reduced dopamine uptake and striatal dopamine transporter binding (Hasler 2010). Another hypothesis is that the corticotrophin-releasing hormone (CRH) plays a prominent role in depressed patients with a childhood trauma. Cortisol is released in the plasma since corticotrophin secretion is induced due to CRH release in response to mental stress (o.c.).

There is not only a range of possible pathophysiological explanations, but there is also a range of possible symptoms such as depressive mood, reduction in interests which seemed enjoyable before, insomnia or hypersomnia, weight loss or gain, etc. (APA 2013). The discussion around the broad criteria in the DSM implies that we live in a society in which more and more people seem to be suffering from depression. This increased number of sufferers might result in an increase in the number of patients for DBS as well. A main point for discussions is why the diagnosis of depression has been increased over the last decades. Is that due to difference in perspective over time, creation of the DSM, or are there any other reasons? According to Dehue (2008, p. 17) three main factors behind the increase of diagnosed patients with depression can be categorized as follows:

1. Depression is an age-old biological disorder, existing in people from all over the world. This increase of the number of patients is caused by new and better diagnostic tools and treatment methods.
2. It serves as a “product” created by the pharmaceutical industry which gains more money and power by selling their products and seeks a way to foist depression into society’s core.
3. This society, a caring society, makes individuals oversensitive with possible help for everything and all their problems. Individuals therefore lose the ability to take care of themselves.

From Dehue’s (2008) point of view we can conclude that it is possible to see the rise of the number of depressed individuals as the result of a biological perspective as well as a societal or cultural perspective. With exception of the first, the other two reasons would probably not influence the development and embedding of DBS for depression. Depression can be seen as something natural and objective without values. The disorder can be deduced from facts, which are identified with the use of scientific research (Boorse 1977). Contrary to the view point of Boorse (1977), Nordenfelt (2007) has adopted a more subjective stance towards depression. He has articulated a normative and subjective theory in which he defines health as the ability to reach essential goals in normal conditions. In this way, a person will have to reach a certain level of well-being and happiness.

Although objective and subjective are the two opponents, a disease can also be defined by society’s views. There are actually different norms and values that influence the perspective on what is considered as ‘normal’ and what is not. The definition of depression depends on the values and norms

developed within a society/culture, what is seen as good or bad, normal or abnormal, and desirable or undesirable. A disease cannot be determined without a societal context and that makes a social constructionist argument (Schermer 2013, p. 124-125). Schermer (2013, p. 117-118) also argues that it is important for the patient as well as for the physician to have a 'label'. For the patient it is a way of recognition and accepting their disorder, and labeling is a way to determine the specific medical area that constitutes a disease. This last includes the acceptance of certain treatments specific for the disorder.

Overall, depression may possibly be considered as biological disorder with societal components. This can be compared to the three statements for the increase of the number of depressive individuals given by Dehue (2008, p. 17). Taken the current views on depression into consideration it is seen as a disease which belongs to the medical spectrum of psychiatry. Over time, there was a search for an explanation why specific individuals were 'different'. People were judged differently due to the label melancholia or depression, but currently depression is situated within the category of brain diseases, a mental disorder for which we seek treatments. This includes that it requires diagnosing and treatment protocols which I discuss in the following section. The changing explanations for depression might influence the treatments developed and the desirability for specific treatments. The idea of DBS for depression presumes a disorder in the brain. The search for brain regions involved in the disorder might make the technology less desirable, this is discussed in more detail in chapter four.

2.2 Diagnosing and Treatment procedures for Depression

Three related but distinct terms are "illness", "sickness", and "disease". Susser (1973) proposed to use the term "illness" to refer to the subjective sense of feeling unwell. It refers to someone's personal experience and not to the pathology of the disorder. "Sickness" refers to socially and culturally held conceptions of health conditions influencing the way someone presents his symptoms (o.c.). Disease implies a focus on the pathological processes that can result in symptoms (o.c.). A physician mainly focuses on a disease as an outbreak of physical symptoms and examines or questions the illness through the patient's experience. This explanation of these three concepts is used in this thesis, in which depression is considered a disease, equivalent to the view of current practices. This means that depression has underlying pathological processes that produce symptoms. However, depression is not only pathological in nature. Considering the aspect of "sickness", there is a social and cultural influence on feelings of depression. Not only the pathological factors, but also the social factors are taken into account to determine whether someone has an illness. When someone expresses the illness, the physician will question the patient and come-up with a diagnosis.

A treatment plan is required after diagnosing individuals who suffer from depression. I outline the current ways to diagnose and treat depression in the following paragraphs. This current perspective of diagnosing and treating depression can be used especially in the social usability part of the

assessment in this thesis. The protocols can give a view about the procedures and possible reasoning. This current perspective can also assist in the development of a protocol including DBS.

2.2.1 Diagnosing Depression

One in ten citizens of the Netherland's population suffers from a form of depression according to stats, and this number has increased over time (Dehue 2008). According to the International Consortium of Psychiatric Epidemiology (ICPE) surveys in 2003, the prevalence rates for depression differ worldwide. In the Netherlands, there is a lifetime prevalence of depression of 15.7 %–this is comparable to the prevalence in the United States which is 16.9 %, the highest prevalence worldwide. In Germany the prevalence is 11.5 %, which is just a bit lower than in the Netherlands. Worldwide, Japan shows the lowest prevalence which is just 3.0 %. (Andrade, Caraveo-Anduaga et al. 2003).

Nowadays, there is an incidence of 700,000 citizens in the Netherlands each year (Elgersma, Bockting et al. 2011), which equals to an incidence of 4.1 per 100 citizens. Although the prevalence in Germany is a bit lower, the incidence is 5.0 per 100 citizens and the incidence in the Unites States is 3.0 per 100 citizens. The highest incidence is found in New Zeeland, with a 5.8 incidence per 100 citizens, and the lowest is in Taiwan–0.8 per 100 citizens (Weissman, Bland et al. 1996). In terms of distress and medical costs, over twenty years, depression will be one of the main primary disorders of concern in the Netherlands, next to cardiovascular diseases (Smit 2009). One possible reason is that this increased emphasis will enable us to better diagnose and study depression. However, it is still challenging to diagnose someone with depression with full certainty (Terluin, van Hout et al. 2004).

DSM-V of the American Psychiatric Association (2013) is a worldwide recognized manual used to diagnose depression according to a specified set of rules based on occurrence of presented symptoms. Additionally, in the Netherlands, the standard suggestion is to diagnose patients according to the DSM manual (Terluin, van Hout et al. 2004). A person with symptoms of depression is expected to visit his General Practitioner (GP) first. The GP investigates whether the symptoms are possibly caused by a depressive disorder, or whether the individual suffers from an underlying physical disorder, or an underlying past event that has caused him sadness or grief which can cause similar symptoms with depression (FPG 2012).

The DSM-V manual defines depression as a state of unusual dreariness and/or loss of pleasure, which persists for at least two weeks. Besides these two main symptoms of depression, the individual should suffer from five or more of the following symptoms during the same period (APA 2013):

1. Depressive mood almost all day, daily
2. Clearly reduced interest in pleasurable activities almost all day, daily
3. Unintentional weight loss or weight gain, or reduced or increased appetite
4. Insomnia or hypersomnia almost daily
5. Agitation or inhibition almost daily

6. Fatigue or loss of energy almost daily
7. Feelings of worthlessness or inadequate guilt
8. Decreased ability to think, concentrate, or decision making
9. Feelings of despair, thoughts or fantasies of suicide, with or without a specific plan.

DSM-V also mentions that these symptoms should not be caused by somatic causes, such as hypothyroidism, mourning, or drugs and they should cause significant suffering or limitations to function in society (APA 2013).

Van Weel-Baumgarten et al. (2012) explain the anamnesis process and physical examination guidelines according to the NHG-standard. The first questions the GP has to ask are whether or not an individual has a dreary mood or depressed feelings, and whether or not the individual expressed a loss of interest and pleasure. This covers the two main symptoms. If both questions are denied, then there is no reason to suspect depression. When one or both questions are confirmed, the GP has to ask whether the patient wants expert help to overcome these feelings or not (o.c.). The next step is the further exploration of symptoms. The GP will then ask the patient for possible causes of complaints and his feelings and examine which symptom the patient mostly experiences, as well as the way he handles it during the whole situation (o.c.). Diagnosing depression can be difficult and this is especially true in the case of mild depression (Terluin, van Hout et al. 2004). In the case of the diagnosis or non-diagnosis of possible mild depression the advice by Terluin et al. (2004) is to repeat the anamnesis process one or two weeks later, to review the findings.

2.2.2 Treating the Disease

Depression is a chronic disorder, but in most cases treatment is administrated as if it is a cure (Elgersma, Bockting et al. 2011). As described in section 2.1, there is a whole range of possible underlying mechanisms involved in the outbreak of this disease. The pathophysiology is probably different between patients, meaning that ‘one-size-fits-all’ treatment is not a good option. Besides the heterogeneity, another problem is that many times, following a period of treatment and recovery, 80% of the patients will suffer from recurrent depression (Bockting 2009). After diagnosis, as described in the previous part, different treatments could be advised. The current expectation is that DBS will take a spot at the very end of the treatment possibilities, thus a patient needs to undergo many other treatments before DBS becomes an option at all.

Antidepressants or psychological treatments are the most popular treatments, but there are many other alternative options to treat individuals with depression. Dehue (2008, p. 15) lists some of the options for the treatment of depression. She includes cognitive behavioral therapy, hypnosis, haptonomics, acupuncture, light therapy, Electroconvulsive Therapy (ECT), and Vagal Nerve Stimulation (VNS). Kusters (2013) claims that, the most popular method for the treatment of a massive repression of psychiatric disorders nowadays is the administration of antidepressants. In

regards to depression, initially, most individuals will be treated with antidepressant drugs (o.c.). However, the psychiatric treatment guidelines of the Netherlands and the health care practice, as used in patient assessments, are not in agreement with that claim. This is because the treatment of a Dutch patient with a diagnosis of depression many times starts with counseling.

2.2.2.1 Treatment Guidelines

In the Netherlands, guidelines for the treatment of depression are defined by the GGZ, which is a national organization for mental health care providers. I elaborate on these guidelines to understand the procedure and evalute the possibility to add DBS in this accepted protocol. The standard procedure is that a GP should start with a treatment plan for the mild symptoms of depression which implies that most of depressed patients will be initially treated by their GP (Katon and Schulberg 1992). When the symptoms of depression persist and the patient does not respond to regular treatment, a GP may refer the patient to a psychiatrist.

The following guidelines are based on the GGZ's multidisciplinary guidelines document from 2013. Before this type of treatment the patient had been subject to one treatment procedures:

1. Depressive episodes, light, first episode which is shorter than three months.
2. Depressive episodes, light, first episode which is longer than three months or recurrent.
3. Depressive episodes, (mild) grave, first episode.
4. Depressive episodes, (mild) grave, recurrent.

The first basic intervention for all groups is psychoeducation. A patient will learn to recreate a schedule for the day, which can include the adoption of a more active or healthier lifestyle. An active attitude is stimulating for the recovery of depression. The progress and depressive episodes of a patient are actively monitored during this psychoeducation. The idea behind this as given by the NHG (van Weel-Baumgarten, van Gelderen et al. 2012), is that depressive symptoms are in most cases transient. In 60% of all cases, the patient is recovered after six months.

Besides this basic treatment intervention, a patient may receive other treatments afterwards, which are based on the treatment procedure of the classified forms of depression. The intervention steps for the group of patients diagnosed with light depression and a first episode lasting shorter than three months, according to the GGZ guideline (2013), include bibliotherapy, self-help and self-management (possibly combined with e-health interventions), active supervision, physical exercise (such as running therapy), counseling, and/or psychosocial intervention. These first-step treatment interventions are taken in consultation with the patient, and evaluated after three months. When there is little to none recovery or improvement, the patient can be subject to the next treatment procedure. Besides the first-step interventions, the patient can choose problem solving therapy or short term treatment. This is evaluated after a period of six weeks. When there is little to none recovery noted, the patient can choose to receive cognitive behavioral therapy or psychodynamic therapy. After a period

of 4 months, a second evaluation will take place and if the patient still suffers from depression, the psychotherapy will continue for longer or pharmacotherapy (administration of drugs) will start.

This is again evaluated after a four month period, and the patient is expected to have recovered completely or else he may try another treatment method. The choice between psychotherapy and pharmacotherapy can be made in first stage. The treatment evaluation takes place after four months and may include the option to continue with the same treatment or start a combination of psychotherapy and pharmacotherapy, a different dose of pharmacotherapy, or a more intensive treatment procedure which may include ECT. The steps taken for the patients in the fourth group, recurrent (mild) grave depression, are similar to the steps of the third group. Concluding from this extensive protocol, a patient with severe depression is subject to a long treatment process. When DBS takes a position at the end of this protocol, probably after ECT, the treatment procedure extends. This might have consequences for the desirability of such a long process, but it is also possible that this extra option give the patients hope for an improved state of their depression. These issues are discussed in the fifth and sixth chapter. I will first discuss the commonly used therapeutics to give a comprehensive image of the current procedures with their positive and negative sides.

2.2.3 Pills or Talking?

Through the study of Dutch guidelines, we can conclude that there are many different options for the treatment of depressed individual. Pharmacotherapy and psychotherapy are the main treatment options. There are many different antidepressant drugs, but the selective serotonin reuptake inhibitor (SSRI) is the first choice drug prescribed by psychiatrists and it is widely used in many instances and countries (Preskorn, Ross et al. 2004, p. 244; Glannon 2007, p. 16). The SSRI's are designed to modulate the synaptic cleft and increase the uptake of relevant neurotransmitters to restore the normal level of serotonin in the brain (Glannon 2007, p. 14). If a patient has an inadequate response to one SSRI, some physicians ascribe another SSRI fist, but most psychiatrists prefer to switch to a drug with another mechanism of action to treat depression (Preskorn, Ross et al. 2004, p. 242).

Besides the possible positive effects of antidepressants, Dehue (2008, p. 186) mentions many side effects of these drugs like dizziness, nausea and throwing up, headache, abnormal dreams, diarrhea, agitation, anxiety, emotional instability, sweating, tremble, palpitations, and electric shocks in the head. Although there are many possible side effects, the continuation of antidepressant drug therapy for depression, following the initial treatment procedure is recommended. This continued treatment process is basically a mean to consolidate the response and lower the risk of relapse (Olfson, Marcus et al. 2006). However, Elgersma et al. (2011) argue against the extension of pharmacotherapy, because of the treatment adherence to drug therapy. This is the main problem as 70-80 % of the patients will stop in one year and 50 % in two years. Another problem with the prolonged treatment

with antidepressants, is the possible debilitation of their working mechanisms over time. Patients should not rely on maintenance doses of antidepressants, but they should receive psychological treatment instead (o.c.).

Cognitive behavioral therapy and pharmacological therapy are considered to be equally effective in the treatment for depression. However, the post-therapy effectiveness of cognitive behavior therapy is higher than pharmacotherapy in patients with mild to severe depression (Dorrepaal, van Nieuwenhuizen et al. 1998; DeRubeis, Siegle et al. 2008). Psychotherapy is the collection of a variety of treatment techniques, including psychodynamic therapy, interpersonal therapy, and cognitive behavioral therapy (Goldberg 2014b). When a depressed patient receives psychotherapy, he will consult with a mental health professional to work out the factors that may have caused depression symptoms. Psychotherapy is characterized by an interpersonal context, with all the variables of human functioning involved in therapeutic learning (Strupp 1986). There are no profound side effects of psychotherapy described in literature, and the main concerns are for patients who quit therapy. However, the number of patients with severe depression who stop using antidepressants is similar to the number of patients who choose to quit therapy (Evans, Hollon et al. 1992).

A combined therapy can be given as well, but it is still possible that the treatment may not work, and the patient still feels depressed after treatment. In these cases, some other treatment options may be considered. These options include brain modulating and brain stimulating technologies.

2.2.4 From Electroshock Therapy towards Deep Brain Stimulation

Pharmaco- and psychotherapy are the therapies of first choice in the treatment of patient with depression, but more radical treatments are possible when a patient does not recover. Neurostimulation has made its entrance in the mental health care sector over the past few decades. Nowadays, more and more experiments are being performed and patients are being treated with different neurostimulating therapies. I will discuss possible neurostimuating technologies, accepted or not accepted in the current care of depression, but these technologies will give the background for the experiments and development of DBS for depression.

ECT is the only therapy included in the guidelines as a possible option for the treatment of patients with depression (GGZ 2013). Although the use of electrical stimulation to modify the brain is used since the ancient times, the first modern example of the electroshock as therapeutic application was documented in 1938. Cerletti initially introduced this method of brain stimulation for the treatment of severe psychosis (Cerletti 1940; Guloksuz, Rutten et al. 2014). Nowadays, most people have a negative opinion on ECT, mainly due to films like ‘One flew over the cuckoo’s nest’. However, ECT is considered to be among the safest and most effective and fast-acting treatments for depression (Guloksuz, Rutten et al. 2014). Prior to this choice of therapy, the patient should note a history of

failure to manage depression symptoms with pharmacotherapy and/or psychotherapy. The real mechanism behind the action of this method is currently unknown, but there is some emerging evidence that modulation of the hypothalamic-pituitary-adrenal axis or disturbance in the immune system may influence the response to this treatment (o.c.). The treatment seems to have a fast response rate, but it can result in cognitive and memory dysfunction. The short term memory system will return a few days after the end of ECT, but retrieval of long-term memory can take approximately seven months (Rami-Gonzalez, Bernardo et al. 2001). The fast treatment response of ECT as well as the significantly lower mortality rate compared to patients who receive insufficient treatment or are not treated at all is another advantage. This is due to the fact that insufficiently treated patients have a high chance to die of non-suicidal deaths, for example myocardial infarct (Avery and Winokur, 1976). It is suggested by Avery and Winokur (1976) that ECT is an adequate treatment, which is supported by research findings of Prudic et al. (1990), indicating that 70-90% of the depressed patients have shown a positive response to ECT therapy. However, in the patient cases where antidepressants have failed to respond, ECT will likely fail as well (o.c.).

Besides ECT, different techniques of neurostimulation have started to be developed (Sironi 2011). One example of neurostimulating technology is the Transcranial Magnetic Stimulation (TMS) during which, a magnetic field is being produced (Piccione, Cavinato et al. 2011). This technology compared to ECT, has a better response rate in patients who have failed to respond to regular pharmacotherapy (Goldberg 2014a). The magnetic field is formed through an eight-shaped magnet used to modulate the excitability of the brain cortex, in order to stimulate a specific area for the treatment of depression (Piccione, Cavinato et al. 2011). The smaller and more precise the electric current is, the more loss of consciousness and the higher the risk of having seizure; however, the effectiveness of TMS is lower (Goldberg 2014a).

Another possible treatment for patients with depression is VNS. VNS refers to a variety of techniques used to stimulate the vagal nerve (George, Sackheim et al. 2000). A small stimulator is implanted just under the skin of the collarbone. The bipolar lead from the stimulator goes under the skin to the vagal nerve in the neck, in order to stimulate the brain via electric pulses. Intermittent stimulation of the vagal nerve can alter brain activity by inhibiting neural processes (o.c.). This therapy is not included in the insurance and Dutch medical guidelines, but the FDA of the U.S has approved the therapy in 2005 as a possible treatment option for treatment-resistant depression (Groves and Brown 2005). A research performed by Rush et al (2000), has examined the effect of VNS in the treatment-resistant depression. From the thirty patients included in the study, twelve had shown an improvement in their mood after ten weeks of simulation.

A new upcoming technology is optogenetics. The basis for optogenetic therapy had started in 2005, when it has been discovered that dozens of single-component proteins can be activated by various wave lengths (Fenno, Yizhar et al. 2011). These wavelengths have various ion conductance

regulation properties which operate in neurons lasting from milliseconds to tens of minutes enabling configurations and opportunities for experiments (o.c.). Optogenetics might be applied in the psychiatric fields as well as in other medical fields. However, these approaches to treatment are currently being developed with the use of animal experiments (o.c.) and there is no clinical evidence at the moment to support their efficiency.

2.2.4.1 Development of Deep Brain Stimulation

The technology of DBS has been under development for the last decades. Sankar et al. (2014) argue that DBS has been developed to deliver continuous stimulation to a problematic area in the brain with the use of a pacemaker-like device. The basic technology has been designed, but there is much room for improvement. Over 100,000 patients worldwide have received DBS treatment for different neurological disorders including movement, mood, and cognition disorders (o.c.). The development of DBS devices focuses primarily on the two main elements of the hardware, viz. the battery and the electrodes. Gardner (2013, p. 712) explains that electrodes have been used by clinicians since the 1930s. In those days, the clinicians use this primarily for ablative therapy. This therapy involves the deliberate, precise destruction of various malfunctioning regions within the brain (o.c.). These surgical procedures were crude, and involved broad disconnection of frontal white matter tracts (Lipsman, Giacobbe et al. 2015, p.96). From the 1940s and onward, neurosurgery improved rapidly with a stereotactic apparatus in conjunction with imaging technologies (Gardner 2013, p. 710-712). This apparatus created a decrease in the mortality rate associated with neurosurgery, but the effects of the treatments were irreversible. Although approximately one-third to two-thirds of the patients benefitted from these procedures, the irreversible nature of the procedure caused discrediting and removal from clinical practice in the 1960s (Altinay, Estemalik et al. 2015, p. 345). Since then, the practice of stereotactic functional neurosurgery has been very limited.

Altinay et al. (2015) discuss that researchers continue their search for a procedure that is revisable and has a low mortality rate. Medtronic was, in 1968, the first to develop a neurostimulator device based on their earlier development of the cardiac pacemaker (Gardner 2013, p. 714-716). The first of these neurostimulators were implanted in the spinal cord, cerebral cortex, and areas deep in the brain such as the thalamus in the 1970s. These clinical experiments with DBS showed positive results. During this time, therapies for a range of conditions that had responded to ablative therapy before, including severe depression incorporate these neurostimulators (o.c.). The material qualities, such as size, biocompatibility, and ability to deliver precise electrical stimulation, are developed to make it possible to adopt and used in health care. However, problems were not unusual; for example, complications caused by the implantation or the power source could fail. The use of lithium batteries and the development of new neurostimulator leads based on the design of endocardical leads made it possible to overcome some of these obstacles in the 1980s by (o.c.). As Blume (2010, p. 34) argues, the diffusion of the neurostimulator was linked to the success of the cardiac pacemaker.

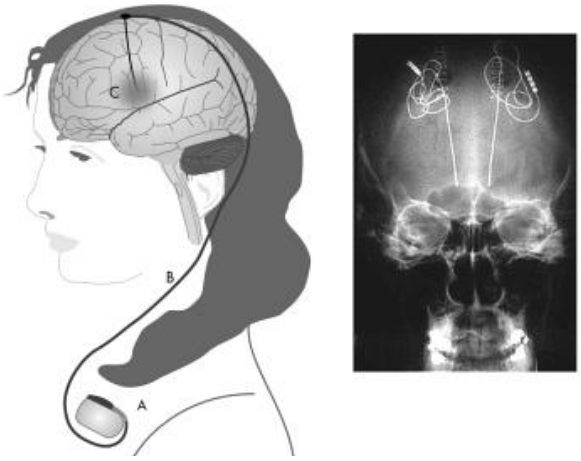

Figure 1. Deep Brain Stimulation. The left picture is a schematically represented impulse generator (A), extension wire (B), and electrode (C) in the subcortical region of the brain. The right picture is an X-ray image after implantation. (George, Higgins et al)

Altinay et al. (2015) argue that the primary advantage of DBS over brain surgery is that there is no need to destroy parts of the brain, due to the ability to start and stop stimulation when desired. When the stimulation stops, the effect stops and the stimulated brain region remains intact, making DBS a reversible treatment (o.c.). In the 1990s high frequency electrical DBS was being used worldwide. During that time, DBS therapy was an option for patients with neurological movement disorders, epilepsy, chronic pain conditions, and headache disorders (o.c.). Amongst others, Benabid (2003), Kern and Kumar (2007), and Gardner (2013) state that this technology can be beneficial for other targets and disorders. I will discuss several experiments with DBS for depression in chapter four.

A currently experimental goal is the treatment of depression with DBS (Piasecki and Jefferson 2004; Galvez, Keser et al. 2015). Findings by Piasecki and Jefferson (2004) that DBS introduces complications such as depression and deficits in oral skills, were linked with the stimulation of the subthalamic nucleus. On the contrary, stimulation in other regions of the brain such as the subcallosal cingulate gyrus can reduce symptoms of depression (Lozano, Mayberg et al. 2008). To understand all these findings better, a broader evaluation of this technology is necessary.

According to George et al. (2000), DBS is the most anatomically discrete and most invasive method to stimulate the deep structures of the brain. As Figure 1 shows, the DBS device consists of three different parts: the impulse generator, the extension, and the electrodes (George, Higgins et al. 2011, p. 318). A thin electrode is inserted directly into the target region of the brain. Electrical currents are transported to various depths in the brain region and these currents can be adjusted externally to optimize the desired effect (o.c.; George, Sackheim et al. 2000). MRI scan can help locating the region for implantation and the more precisely the location is defined, the better the results. As Schuurman et al. (2014) explain, two holes are drilled in the skull through which the electrodes can be implanted. The wire extensions of the electrodes run through the neck and attach to the impulse generator, which is a battery operated device mostly placed underneath the clavicle (George, Higgins et al. 2011, p. 318). The placement of electrodes is tested during the operation, which means that the patient needs to be awake during the procedure.

The settings for the stimulation have to be programmed after the operation. This is a trial and error phase to test different settings and determine the desired settings as well as minimize any

negative side effects (Schlaepfer and Lieb 2005; Kern and Kumar 2007). Physicians can mold the stimulation and thereby its effect, by stimulating slightly different parts of the brain. The effects have to be evaluated by considering the actual effect on the patient (George, Higgins et al. 2011, p. 319). Physicians cannot only choose which electrode will emit the electrical current, but they can also change other parameters for a different effect lie for example the voltage, pulse width, frequency, and duty cycle (o.c.). The frequency in this case seems important, as a low frequency seemed to have no beneficial effect at all (o.c., p. 319-320). The optimal setting for the treatment of depression is still in an experimental phase and can differ from patient to patient (Galvez, Keser et al. 2015). I discuss the search for the optimal stimulation settings further in chapter five.

Besides this ability to make the treatment personalized and specific for each patient, there are also other additional advantages of the DBS method. Although it is invasive, the reversibility of DBS gives it a comparative advantage over other brain surgery treatments. Symptoms immediately remit when a surgeon stops the electric current or moves the electrode towards another position (Bejjani, Damier et al. 1999; Schlaepfer and Lieb 2005). Even removal of the thin wire, leaves the brain largely unchanged–unlike the process of resection (George, Higgins et al. 2011, p. 318). Lozano et al (2008) argue that DBS is relatively safe because there are no serious adverse effects and no history of permanent deficits. According to their findings, the procedure was tolerated well by the patients who tried it with sustainable benefits being noted in one year. This study has shown the effects in the experimental phase of this therapy, but any long-term effects of using DBS for the treatment of depression are currently unknown (Galvez, Keser et al. 2015). Long-term effects in patients with Parkinson's Disease for example, have been investigated and have shown subtle findings. Mild gliosis can be found around the electrode and moderate cell loss at the tip of the electrode. These local changes though, are not reversible (George, Higgins et al. 2011, p. 322), and possibly similar in the treatment of patients with depression.

This description of DBS is just a general introduction on the technology with its main elements. More details about the experiments and technological possibilities for the treatment of depression are discussed in chapter four. That chapter considers the technological feasibility, including possible developments of the hardware and implantation. Chapter five will continue with the various hypothesis for research and the embedding of the technology, including the phase of changing stimulation settings.

The different neurostimulating therapies mentioned in the previous parts of this section, are shown in Table 1 (George, Sackheim et al. 2000). A comparison between regional specificity, clinical applicability, and invasiveness is also being made. A current difference with this table is that the clinical applicability of DBS is now approved for the treatment of refractory Obsessive Compulsive

Table 1. Current and potential interventions for the treatment of depression. Comparison based on regional specificity, clinical applicability, and invasiveness (George, Sackheim et al. 2000).

Somatic intervention	Regionally specific?	Clinically applicable?	Invasive?
Electroconvulsive therapy	++ (+++ if induced by magnets	++++	++ (anesthesia, generalized seizure)
Transcranial electrical stimulation	+	++	+ (scalp irritation)
Transcranial magnetic stimulation	++++	+++ (clinical trials underway)	+ (painful at high intensities)
Vagal nerve stimulation	++ (discrete brainstem nuclei initially, unclear if different parameters selectively involve other brain regions)	+++ (on the market for epilepsy, clinical trials in depression [see Rush et al 2000])	+++ (surgery for generator implant)
Deep brain stimulation	++++	+++ (approved in the United States for treatment in movement disorders, pain syndromes; no work in depression yet)	++++ (brain surgery)

+, a little; ++++, a lot.

Disorder patients as well (van Westen, Rietveld et al. 2015), and that VNS is approved by the FDA as treatment for depression (Groves and Brown 2005). Compared to ECT, TMS and DBS are regionally specific which is useful for overcoming possible side effects. TMS and DBS are both (possibly) clinically applicable, but DBS is far more invasive. At the moment, both technologies are experimental for depression which makes it difficult to compare clinical findings. The advantage of DBS for depression is that specific stimulation in deeper regions of the brain is possible. As LeDoux (2003) argues, this is beneficial because of the deeper site of the emotionally important area–the forebrain of the limbic system.

2.3 Concluding

This chapter has shown that the concept and comprehension of depression has changed over time. The historical perspectives examined, portray the disorder as something that has been already present since ancient times. At first, melancholic people were seen as different, but over time other explanations (mainly physical) have been sought out. Within the search for physical root caused, depression was later defined as a disease, a mental disorder. Depression is embedded in the current health care system, for which there are guidelines to diagnose and treat the disease. The diagnosis can be made with the help of different categories, of which DSM is mostly used worldwide. For the treatment of depression, different countries have different treatment protocols. In the Netherlands for example, the treatment will start with basic interventions such as self-help and physical exercise regimes. If these treatments do not prove out to be beneficial, a physician in consultation with the patient may choose pharmacotherapy and/or psychotherapy. The treatment procedure is strict according to protocol and 'new' technologies need to become accepted and embedded in the protocol before use. However, new

technologies are under development and seem required for the treatment of patients who otherwise do not recover.

The use of neurostimulation is experimentally allowed, but only ECT is included in the current protocol. ECT is the last possible option for the treatment of patients with depression, which implies that patients who do not recover after ECT, may not have any other alternative treatment options. This leads to the research for other treatment options such as other neurostimulating technologies. There are studies concerning different neurostimulating technologies used to treat treatment-resistant depression, but these are still in an experimental stage and have not been officially approved for treatment outside experimental settings. One such high-tech treatment is DBS, which is still labeled as 'experimental'. DARPA sees a future in the development of this technology as treatment for depression and possibly as preventive treatment for military personnel. In spite of other clinically applicable neurostimulating technologies, DBS seems to have advantage for treatment of depression due to the direct stimulation of deep brain regions.

3. Assessing the Plausibility of Expectations

DBS have been used in several experiments to investigate the treatment possibilities for patients with treatment-resistant depression. These experiments result in possible expectations implying the desirability of such a high-tech treatment. I discuss whether the promises and expectations require further evaluation, and why I will discuss the plausibility of these expectations. A theoretical framework for evaluating the expectations of new and emerging technologies is developed by Lucivero et al. (2011). This assessment is introduced in the first chapter, but I elucidate on that, because it is performed as part of this thesis. I start with a discussion concerning new and emerging technologies and how we can evaluate these technologies in the first two sections of this chapter. Although there are many different possible assessments, I choose to perform an assessment on the plausibility of expectations, as proposed by Lucivero et al. (2011). This assessment will help to distinguish between plausible and implausible expectations to assess the desirability of DBS for depression. The approach is discussed in the third part of this chapter.

3.1 New and Emerging Technologies

DBS is a current accepted technology for several indications, but it seems that these indications will extent. For example the use of DBS for depression is a possible new and emerging technology. I start with this discussion with a background for the possible difficulties during development and embedding of new and emerging technologies. As Brey (2012) defines, new and emerging technologies are still under development or at the stage of experiments. Technological development and social uptake of technologies is different for each technology. On one hand, some technologies belong on an early stage of development and are far from being introduced into society because its benefits and issues are not visible in practice (o.c.). For example, optogenetics is a possible treatment for patients with depression, but all ideas are theoretical and not based on real practical experience. On the other hand, some technologies have already been introduced in practice, making it possible to analyze and evaluate the benefits and ethical issues emerging from their use. However, the practice with additional benefits and risks in one case can be very different from another case (o.c.). For example, in the case of new treatment possibilities with DBS, rising issues with a treatment for Parkinson's Disease probably differ from issues emerging from the treatment of depression. Overall, considering both new technologies and new practices, the benefits and concerns are not clear in practice, making their evaluation difficult.

To increase awareness and caution, Davis (2011) created a growing list of new and emerging technologies launched. This list contains the technologies that might lead to national or international implications. An important advantage is knowing which of these technologies or innovations need evaluation and further adjustments in the future. The challenges introduced by emerging technologies

can occur in different components of technological innovation. Brain implants constitute a part of the list of new and emerging technologies. The underlying mechanisms of DBS exist, but the application process may vary when using a certain technology for a different group of patients. For example, a group of patients with psychiatric disorders are being treated with DBS to suppress certain feelings or thoughts, whereas in patients with Parkinson's Disease DBS may be used to suppress tremor symptoms.

3.2 Assessing New and Emerging Technologies

To investigate the expectations about DBS for depression, I used an assessment for new and emerging technologies. There are many different approaches for the assessment of new and emerging technologies. Before I elaborate on the method used for this thesis, some other methods are initially discussed. These other methods form a larger picture of (ethical) assessment and provide an opportunity to compare with the method used in this research. Jakeman et al. (2006) claim that the steps that have to be taken for the development of a technology, vary slightly from case to case, but every stage should be subject to critical analysis of all benefits and concerns. There is, for example, a difference between the introduction of new medication for the same patient group and the introduction of a new technological treatment. In the first case the risks, benefits, and costs have to be analyzed, but a path leading to practice must be apparent already. With the introduction of a new technology, the risks, benefits, costs as well as the possible embedding of the new technology should be analyzed.

Banta (2009) defines Technology Assessment (TA) as "a form of policy research that examines short and long-term consequences of the application of technology" (o.c., p. 7). The goal is to provide policymakers information on alternatives gained from assessments. TA is an extremely broad field with multiple activities assessing the technology as well as the diffusion of the technology, its acceptance, and its role within society (o.c.). Health Technology Assessment (HTA) is an assessment method to evaluate emerging technologies within the medical domain. Banta and Perry (1997) explain that the idea behind HTA, is to enlarge the evaluation process and investigate the clinical consequences as well as the economic, social, or ethical implications of the new technology. HTA is usually performed to analyze all the consequences of emerging medical technologies, but the main focus is on cost-benefit, which analyzes the change in benefit compared to the change in costs (Goodman 2004, p. V-2). Ten Have (2004), concludes that there is a clear gap between ethical considerations and TA. Ethical evaluations can definitely contribute to the analysis, and for this purpose we need to go beyond the technological framework and investigate any moral issues emerging from the use of this technology (o.c.).

To overcome this lack of ethical considerations embedded in the approach, there are different TAs that attempt to take ethical aspects into account. Ethical problems introduced by the rise of a new technology tend to be unknown, even with the use of TA tools. An approach with the purpose to

demonstrate early indicators of negative ethical implications is necessary according to Palm and Hansson (2006). In this context, they propose a method based on an ethical check-list. Ethical Technology Assessment (eTA) proposes nine important groups that should be considered during the research and design, and the implementation of new technologies (o.c., p. 543-544; 551-555).

1. Dissemination and use of information
2. Control, influence, and power
3. Impact on social contact patterns
4. Privacy
5. Sustainability
6. Human reproduction
7. Gender, minorities, and justice
8. International relations
9. Impact on human values

These items are possibly also important for the evaluation of DBS, but the problem is that new technologies may lead to unidentified ethical issues, which can cause problems to the full integration into society. Questions such as "How should we use this technology?" may arise and become part of the (ethical) discussion procedures (o.c., p. 543-544). The idea is that these ethical issues have to be examined and dealt with from an early stage, like for example during or before the planning/designing process. When this is followed, the differences between social values and technological potential may become less contradictory (o.c. p. 548). The problem of uncertainties, as introduced in chapter 1, does not seem to be solved with this method. It gives guidelines for ethical analysis, but ideas about future states of the technology are still uncertain and probably speculative.

There is the problem of uncertainty and taken for granted expectations, but how could we deal with this? As Brey (2012, p. 2) argues, "emerging technology is technology in the making", which means that many aspects of the nature and consequences of a technology are under discussion, and the ethical issues emerging cannot be clearly identified. Brey (2012) suggests two different approaches to deal with this uncertainty. First, the ethicists have to be aware of the uncertainty and restrict themselves. The analysis should be based on the qualities of the technology that are likely to manifest themselves in all aspects of its use. Secondly, ethicists should rely on existing predictive studies, to study the possible ethical implications of a technology and its social consequences (o.c. p. 2-3). However, both approaches seem inconvenient for the assessment of the expectations of DBS for depression. The first approach for example, is too limited. When an ethicist only focuses on the general qualities of the technology, many specific implications might be ignored. The ethicist may limit himself to a known set of technological possibilities that seem applicable. This can become challenging with the use of DBS for depression, because the disorder and the brain are no similarly set in all cases. It is possible that the technology may have the same performance in all cases, but this will not lead to similar results with all different applications for different diseases. Regarding the second approach, knowledge can be acquired from the performance of DBS in patients with Parkinson's

Disease and be later used in forecasting studies, but all this knowledge and the results of the treatment should be based on the implantation in a different area of the brain with a different intended result.

The different TAs and proposed solutions to overcome uncertainty surrounding this area can support the discussions concerning ethical issues of new and emerging technologies. A main consequence of assessments based on speculations about a certain technology, is that researchers may discuss these ethical implications or promises for the future more forcefully. This may cause bias towards the overall perspective of a technology under development, including all of its promises and concerns. As already discussed in the introduction, Nordmann and Rip (2009) call for fewer speculations, because there seems to an excess of speculative ethics based on hypothetical scenarios for the future, with no real or tangible evidence. To overcome this possible problem and deal with the uncertain areas of DBS for depression, I will analyze the plausibility of the expectations, with the use of an assessment developed by Lucivero et al. (2011), to investigate how we could assess the desirability, and which issues we should take into account.

3.3 Assessing Plausible and Implausible Expectations

Ljungblad et al. (2011) discuss that researchers will contribute to ethical discussions which lead to ethical speculations on possible issues of the technology in the future. Speculations and the ethics of speculations have already been noted in 1902 when Ryan defined ethical speculations as "transactions that are made for the sole purpose of getting a profit" (Ryan 1902, p. 335). He has regarded speculations as a widespread evil for society, which can sometimes be deceiving (o.c.). Speculations can be based on expectations of a new and emerging technology. As mentioned already, according to the Merriam-Webster dictionary, an expectation is (1) "a belief that something will happen or is likely to happen" and (2) a "feeling or belief about how successful, good, etc., someone or something will be." The above definition shows that an expectation consists of different parts i.e. a predictive and more factual aspect and a normative element. These two parts will be reconsidered on the assessment method used in this thesis.

I will evaluate the plausibility of the expectations about DBS for depression, because expectations based on speculations of a new and emerging technology can often lead to speculative ethical aspects. Questions like "Which challenging technology really needs our attention?" or "Should we discuss possible actions and dilemmas that may be faced with a new technology?" should be answered in an effort to analyze the plausibility of an expectation before further discussion. This analysis can be used support the control of speculative ethics. As already described in the introduction, anticipatory ethics and the excessive attention to ethical aspects can result in highly speculative scenarios (Nordmann 2007). Speculative ethics may invite a call for action regardless of how plausible an expectation really is.

3.3.1 Methodology of the Assessment

Nordmann and Rip (2009), argue that development will call for a reflection on different ethical implications. Swierstra and Rip (2007), argue that when a prediction is too much speculative it can affect the further development of the technology. When new and emerging technologies are still under development, it means that it is possible not only to discuss the desirability and feasibility of an innovation, but influence their development as well (o.c.). Lucivero et al. (2011) develop one possible assessment to 'test' the plausibility of expectations. The assessment of the plausibility of these expectations introduced with the research and development of new and emerging technologies requires skepticism and logical evaluation (o.c.). This assessment focuses on three different parts which are inherent in the nature of an expectation; technological feasibility, social usability, and desirability. Taken the definition of expectation, the above three parts are already present there. The definition consists of two parts, but technological feasibility and social usability stems from the predictive part and the desirability stems from the normative part. This chapter will continue with a description of the focus of each step and the next three chapters will include an evaluation of the different steps used in the assessment of the plausibility of expectations of DBS for patients with depression.

3.3.1.1 Technological Feasibility

There are many different reasons why we should not trust most scientists, or more specifically why we should not trust all published literature by these scientists. In many cases, existing literature focuses only on the positive outcomes. As King et al. (2011) argue, the scientific field might cause hype and there are possible underlying interests for conducting a study .e.g. to gain funds for research. From the study of history of such methods, it is apparent that many expectations have never been materialized and they have been made mainly to gain financial research support (o.c.). The target audience is a very influential factor, and the arguments the scientists raise seem to be convincing for this specific audience group. To overcome this problem, Brey (2012) suggests that the engineers of a new and emerging technology are the ones that should inform ethicists about the possible risks of this technology. This is possible by performing research on the laboratory floor as Lucivero et al. (2011) suggest. It seems that whenever scientists overestimate their predictions, ethicists tend to overestimate the ethical issues surrounding these predictions. An analysis of these expectations is necessary due to the fact that ethicists are considered less qualified to evaluate any technological predictions (Roache 2008). An ethicist will likely come across these problems and uncertainties rose by the scientific field, and should investigate each expectation for its plausibility. I will investigate the expectations of future developments with DBS in the fourth chapter of this thesis.

Lucivero et al. (2011) argue that an ethicist can explore the expectations in their familiar context which is less tainted by strategic considerations compared to proposals raised for gaining research funds or published literature with mainly positive results. The ethicist here needs to become more aware of the current development and the plausibility of the expectations (o.c.). I have used

literature and information from the interviews to assess the plausibility of the expectations about the technology. The ethicist needs to use acquired information to determine whether or not the expectations need reconsideration. Prospective insights can be used to analyze the use outside experiments (o.c.). However, an expectation is not only about the technological feasibility and thus, ethics should not only focus on the technicalities, but also on the conditions regarding use and need.

3.3.1.2 Social Usability

Different designs and applications of the same technology might pose different ethical implications and affect society and imagined users differently. Nordmann (2007) argues that the evaluation of the effect a new technology may possibly have on the society, might lead to scenarios which could undermine further research. The need for evaluation of the technological possibilities goes back to the previous component (technological feasibility), but there is an emerging need to study the expected use and performance in societal practices as well. Presuppositions are used within the evaluation of this step, based on the way society operates and the practices in which a specific technology probably becomes embedded (Lucivero, Swierstra et al. 2011). Future implications identified for a certain technology can differ from the implications related to its actual use. These implications related to the actual use of the technology, may shed further light on the existing practices of people in everyday life. As suggested by Lucivero et al. (2011), we need to evaluate imagined embedding scenarios. Assumptions should be made regarding the intended users and we need to address multiple questions to determine their involvement during the embedding process of a new and emerging technology. We basically want to uncover the fictive script of an emerging technology. This can be done by exploring the current and envisioned context of an application by all different actors (o.c.).

A broad description can be made, which points to the social conditions that are implicit in the expectations and helps to envision the new technology within the social context (o.c.). I describe a description of the current care of patients with depression and a possible script of DBS for depression in the fifth chapter, based on the current experimental settings and information obtained during the interviews. These broad descriptions can be used as a tool to envision the expectations of emerging technologies in society. Furthermore, these scenarios demonstrate the possible envisioned use of the technology, broaden understanding and define the way actors should adapt to a new device (o.c). To assess the plausibility of the conditions, it is useful to collect information about the knowledge and experience of the intended users of the technology.

Lucivero et al. (2011) argue that it is possible to discuss whether or not there is a need to adapt to an emerging technology based on this user analysis. Besides this, it is possible to contribute to the expectations and prevent certain uses or encourage new uses of the technology in another case. The assessment of social usability might contribute to reveal all of the bottlenecks between developers and user visions as well as to show perspectives of actors and possible new envisioned use of a technology (o.c.). When an assessment of a new technology or an application takes place in an early stage of

research and development, the design and the implementation of the technology can be evaluated better and adjusted towards more desirable situations.

3.3.1.3 Desirability

Lucivero et al. (2011) argue that the focus in this last dimension is solely on the normative evaluation of the impact of a new technology. The claims of technological benefits often come with certain values and moral aspects, which are implied in an expectation. Whether or not an expectation can be accepted as plausible depends on the morality of different actors (o.c.). The main focus in this part of the research is to question whether the morality implied in an expectation is accepted as plausible, according to the morality of different actors. The benefits of the technology at stake are presented within the expectations (o.c.). These expected benefits convey certain values which are not clearly shared or understood by all. When studying people, we need to categorize them into different user groups to evaluate their values. Lucivero et al. (2011) argue that this diversity may be a good thing, because it can show the level of controversy embedded in the development and use of a new technology. The envisioned ideas by users and other actors are taken into account, leading to possible discussions which compare the multiple views of 'good' (o.c.).

The controversies in desirability can be examined by the use of moral argumentation from earlier debates on emerging technologies. These debates can show us a way in which the debates might emerge so we can control them (o.c.). Although we can use existing debates, it is also important to remember that practices may evolve in unexpected ways after their introduction. People are not very good at judging the probability of an expectation and therefore it is unwise to demand development in a social desired direction (Roache 2008). As Nordmann (2007) argues, ethics make it possible to perceive and evaluate the world and technology as something that is not entirely a fictitious future development. We tend to find it hard to imagine ourselves as someone else or entirely changed. If we cannot imagine ourselves changing, can we imagine changing our values? We probably cannot imagine changes that go beyond the existing capabilities of technologies (o.c.).

Lucivero et al. (2011) discuss that it is difficult, but we should explore the unexpected paths. These paths will broaden the vision of scientists and intended users about future technological practices. There is a bounded change between technology, society, and morality. When one changes, there is likely a change noted in the other, which is called techno-moral change by Lucivero et al. (2011). This techno-moral change should be expected, because it is not an exceptional event–it is a duty for the ethicist to make the actors aware of unexpected moral changes due to the creative role of new technologies (o.c.). With the use of the comprehensive descriptions as mentioned in the previous part, we can make actors aware of intended desirable (or undesirable) impacts on society or an individual (o.c.). The descriptions can give us a guideline to start analyzing the more subtle impacts, such as people's daily life, practical routines, or responsibility, and investigating changes in unexpected ways to evaluate whether or not the morality implied in an expectation is plausible. In the

sixth chapter I will analyze several ethical implications discussed during the interviews. However, the values as expressed by the different interviewees are taken for granted, this thesis does not consider changing morality.

3.4 Applying the Assessment in this Research

The assessment described previously will focus on the expectations raised by technological research, design, and development e.g. those presented in the table in Appendix A. The question now is 'Why is this assessment of the plausibility of expectations useful in the case of DBS for depression?' As shown in the introduction, the new application of DBS as a treatment for depression is considered to be a beneficial technique. There are mainly positive expectations and arguments spread in the scientific and public domain about the outcome of research on DBS for depression. There are ethical implications discussed as well, but these mainly concern DBS in general and less DBS specific for depression. DARPA has seized the opportunity to invest in this technology not only for the development of a new treatment for soldiers suffering from Post-Traumatic Stress Syndrome, anxiety, and/or depression, but also as a possible enhancement tool, and a technological tool useful for gaining more knowledge about the human brain. I assume that the suggestion of DARPA, to use the technique as a method to forestall possible mental disorders during or after military service, is too premature. As will be discussed in the next chapter, the possible implications including risks as well as benefits are under investigation and currently uncertain. This is already an issue with DBS as a treatment, but might be influential for the discussion about enhancement as well. The ethical implication of enhancement is discussed in the sixth chapter.

The scientists as well as media depict DBS as a solution for treatment-resistant depression. Apart from the fact that it is not even possible to cure depression, the expectations are based on very small scale studies. The use of DBS within the psychiatric domain is received as something positive, but there is less certainty about the outcome, and especially when it comes to the long-term results of this treatment. Considering the positive messages, DBS seems a beneficial technology, but are its expectations plausible? To answer this question I use the assessment as developed by Lucivero et al. (2011). This research can therefore help to evaluate the plausibility of DBS for depression by taking the near mundane issues into account. The research is performed as described in the materials and method section of the introduction. The literature as well as the empirical part will help to illustrate controversies and identify plausible and implausible expectations. The assessment of plausibility is used to determine how we could assess the desirability of DBS for depression, by identifying the most pressing ethical issues.

4. Technological Feasibility

An ethicist should be aware of influential speculations, and unrealistic expectations, of new and emerging technologies. I have used an assessment to analyze the plausibility of expectations, as developed by Lucivero et al. (2011). They claim, an expectation consists of three dimensions; technological feasibility, social usability, and desirability. To evaluate the technological feasibility, this first part of the assessment, is to investigate the experiments in the scientific field and the specific technology involved. An ethicist should explore the expectations in their familiar context of development; in the case of DBS, the familiar context is the laboratory floor and/or the hospital ward. This exploration might be less tainted by strategic considerations to gain research funds (o.c.). I compare the current technologies and the expectations about the technology and the development as discussed in literature with the expectations discussed by experts during the interviews I performed.

I interviewed different actors, such as the engineers and researchers involved in the development and clinical trials, as well as medical personnel, to evaluate the expectations. The goal of this chapter is to evaluate the plausibility of the technology as well as the expected developments of DBS. After the general introduction to DBS in chapter two, this chapter continues with the current research performed on DBS for depression. After this, I discuss two aspects of the hardware in depth, namely, the electrodes and the battery, and show the discussion of all hypotheses and experiments concerning different brain regions for implantation and stimulation. I use the analysis of literature and interviews to conclude with the plausibility of the expectations of DBS for depression.

4.1 Research to Extend the Indications for DBS

Several experiments used DBS to treat depression over the last ten years or so. One was by Jimenez et al (2005), who performed a study with one patient. They concluded that “The effect of surgery on the patient’s clinical symptoms and signs of depression was dramatic and occurred after insertion of electrodes” Jimenez et al. (2005) say that their presented results are promising for electric stimulation of the inferior thalamic peduncle (ITP) to treat depression. However, results based on one patient with unipolar major depression could be too optimistic. These experiments and the acceptance of DBS for Obsessive Compulsive Disorder brought the branch of neurosurgery back into the psychiatric domain. This reintroduction was discussed during the interview with Physician 3, who said, “We have to do something for the patients who do not respond to any other treatment.” DBS could give an additional treatment option for severely depressed patients. Currently, DBS is in the experimental phase and only performed on treatment-resistant depressed patients. Galvez et al. (2015, p. 60) argue that despite the countless advances in the treatment of depression, treatment-resistance is a main problem. ECT is not efficacious for all patients with treatment-resistant depression. ECT shows to be efficacious in the

acute treatment settings or as a maintenance treatment, but not beneficial for all patients with depression (Rabheru 2012).

This section is a review of the current literature of the experiments with DBS for depression, based on a review by Galvez et al. (2015). They have included ten different papers of experiments with DBS for depression, performed by different research groups. Their review includes most of the experiments published between 2005 and 2014, and I see it as a sufficient overview of the current experimental state of DBS as a treatment for depression. I highlight some of the general claims made in papers, discuss why we should be careful, and not directly accept these statements. Table 2 shows ten studies, as compared by Galvez et al (2015). The overall response rate is 29-100%, but the table shows that additional aspects need to be taken into account besides response rate when interpreting the results. The aspects that differ between the studies are the brain region, the number of patients included, the follow-up period, and the response rate. I discuss these four aspects in this section following Table 2 and end with an overall conclusion.

A broader understanding of the disorder and the underlying pathophysiology is necessary for the investigation on the brain region(s) involved in depression. Different research groups investigate different brain regions (see Table 2), because there is little to no understanding of the brain region(s) involved in treatment-resistant depression. The possibility of using DBS at different target sites resulted in more and more interest in this technology. I will discuss different hypotheses for the choice of brain region and the experiments in section 4.4 of this chapter.

The number of patients included in the different studies is low, ranging from 1 to 21 patients with treatment-resistant depression. Patient selection is difficult because there are multiple inclusion and exclusion criteria; however, there is also no unambiguous definition for treatment-resistant

Table 2. Clinical studies with DBS in treatment-resistant depression. Different research groups investigated different brain regions. Each study had included 'n' patients with treatment-resistant depression. SCG: Subcallosal cingulated cortex, ITP: Inferior thalamic peduncle, VC/VS: Ventral capsule/ventral striatum, ALIC: Anterior limb of the internal capsule, NAcc: Nucleus accumbens, LHb-c: Lateral habenular complex, and slMFB: Superolateral medial forebrain bundle (Galvez, Keser et al. 2015, p. 62).

Author	**Brain region**	**n**	**Follow-up (months)**	**Response (%)**
Mayberg et al. (2005)	SCG	6	6	60
Jimenez et al. (2005)	ITP	1	24	100
Lozano et al. (2008)	SCG	20	12	60
Malone et al. (2009)	VC/VS (ALIC)	17	14-67	71
Bewernick et al. (2012)	NAcc	10	48	45
Sartorius et al. (2010)	LHb-c	2	12	100
Holtzheimer et al. (2012)	SCG	12	24	92
Lozano et al. (2012)	SCG	21	12	29
Schlaepfer et al. (2013)	slMFB	7	3-8	86
George et al. (2014)	LHB-c	2	?	100

depression. It is possible to define treatment-resistant as an inadequate clinical response to antidepressants administered at an effective dose for a sufficient duration, psychotherapy, ECT, or any known treatment combination (Rabheru 2012). Different research groups have different inclusion and exclusion criteria to define the treatment-resistant patient population. This patient selection aspect is discussed further in chapter five. Using this data to form conclusions is difficult due to the low number of patients included. For example, a response of 100% based on a study with one or two patients could be coincidence (Jimenez, Velasco 2005; Sartorius, Kiening 2010; George, Schlaepfer 2014).

A follow-up is necessary in order to investigate the long-term effects of the DBS treatment (Galvez, Keser et al. 2015). The duration of follow-up is very different between the studies. The duration not only differs, but is also short in most studies. Only two studies have a follow-up period of more than two years. There is a follow-up study by Kennedy et al. (2011) based on a patient population included in research of DBS for depression between 2003 and 2006 by the group of Mayberg. They observed 20 patients for one, two, three, and approximately six years after treatment. This follow-up study did not include DBS implantations, it is therefore probably not included in the review of Galvez et al. (2015).

To analyze the improvement, Kennedy et al. (2011) use the Hamilton depression rating scale (HAM-D). This scale is commonly used in research to evaluate the depressive state of patients, and thereby the response to the treatment. HAM-D designed to complete after a clinical interview, but also possible to use to evaluate the depression. It is possible to compare the baseline before treatment with the score at several points in time during or after treatment. Figure 2 shows the HAM-D scores at several points in time after DBS. The follow-up study by Kennedy et al. (2011) suggest that there are short and long-term benefits associated with DBS of treatment-resistant depression; the response rates after one, two, three, and approximately six years were 62.5%, 46.2%, 75%, and 64.3%, respectively (see Figure 2). These results suggest that DBS can be beneficial and effective on a long-term basis.

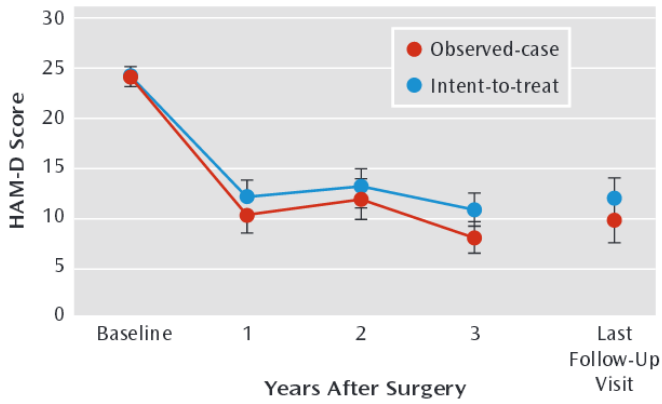

Figure 2. Hamilton Depression Rating Scale (HAM-D) scores for patients with treatment-resistant depression (N=20) at baseline, 1, 2, 3 and approximately 6 years after surgery. Error bars indicate standard error of the means (Kennedy, Giacobbe et al. 2011).

Most of the acute adverse effects caused by the stimulation are mild and reversible when the stimulation stops, or when parameters change (Galvez, Keser et al., p. 66). Table 3 shows the prevalence of the adverse effects documented in newly implanted DBS patients with neuropsychiatric disorders. Galvez et al. (2015) state that further research on short and long-term stimulation of different brain regions is

necessary for the acceptance and incorporation of DBS as a treatment for depression. They conclude that we should approach DBS for treatment-resistant depression as a treatment in the experimental phase (for now). Research should be expanded with larger patient populations and include follow-up research. Such research could provide a better understanding of the brain regions involved with depression and developments required to make the treatment more specific. However, there is a minimal understanding of the brain, the pathophysiology, neuroanatomy, electrophysiology, and neural activity, and the actual effects and side effect of DBS (o.c.). An increased understanding might adjust the treatment, possibly making it patient specific.

In scientific literature there is much emphasis on the positive outcomes of DBS for treatment-resistant depression. During the interviews, most actors have a positive view as well. Physician 2 argues that "We will propose this treatment as a normal treatment for patients with depression when we have acquired more knowledge about the possibilities." Current literature primarily focuses on the outcome of the research, and less on the device itself. The hardware will have an influence on the stimulation and the effects. To investigate the plausibility of the expectation that the hardware improves, I discuss the two most influential parts for stimulation in the following sections of this chapter, the electrodes and battery.

Table 3. Reported adverse effects in 728 newly implanted DBS patients with neuropsychiatric disorders (Galvez, Keser et al. 2015, p. 66).

Serious adverse effect	**Percentage (%)**
Postoperative pain, stress and discomfort	6,6
Lead repositioning	6,1
Stimulation not effective/insufficient tremor control	5,9
Lead migration/dislodgement	3,3
Intracranial hemorrhage	3,1
DBS explanation	2,8
Erosion	1,9
Infection	2,6
Paresthesia	1,4
Component malfunction (IPG, lead, extension)	1,2
Seizures	1,2
Subcutaneous hematoma	1,2
Electrical shocking or jointing	0,9
Headaches	0,9
Lead fractures	0,9
Paresis	0,9
Disequilibrium	0,7
Allergic reaction	0,5
Burr hole ring and cap failure	0,5
Electrode short circuit or open circuit	0,5

4.2 The Technology Behind the Treatment

Researchers and physicians I interviewed had different thoughts about the hardware of DBS. On the one hand, some see the technology as, "The basics are there and it is ready to use" (Physician 3); on the other hand, some actors see areas for improvement. In most cases, a rechargeable battery and electrodes with four contacts are implanted. This technology is indeed ready to use, but engineers are trying to improve it in order to improve the treatment itself. The following section is based on the expectations about the development of the hardware raised during the interviews. I elaborate on the question, 'Which expectations and promises about the hardware circulate in the technological domain?', and discuss the battery and the electrodes. I compare the expectations and arguments in the scientific literature with the issues discussed during the interviews. The next section will consider the discussion about the choice of the brain region for implantation.

4.2.1 Batteries will Die

A primary concern described in literature is the worsening of symptoms if and when DBS is interrupted by stimulator battery depletion (Greenberg, Malone et al. 2010). A dead battery could have a terrible effect on the lives of patients with depression, further discussed in chapters five and six. The expected life of a battery is important, because symptoms reoccur or worsen and re-surgery is required when the battery dies. When this inevitably happens, a replacement surgery is necessary. To complicate matters, it is difficult to predict exactly when a battery will die. Stimulation for psychiatric disorders such as depression requires more energy than the stimulation of movement disorders (Sarem-Aslani and Mullett 2011). Greenberg et al (2010) state that battery depletion occurs between 5 and 13 months with the treatment of patients with Obsessive Compulsive Disorder. When a normal battery is used this means that approximately each year someone needs a replacement surgery. Development of the rechargeable battery might overcome the problem of approximately annual surgery. The rechargeable battery will run out in approximately 7 years, however, the patient has to recharge the battery each day. This is another inconvenience and can become a problem when the patient does not have the time to recharge, and could potentially have a large influence on the quality of life. According to the researchers I have interviewed, the expectation is that it is possible to develop a better rechargeable battery. The desired battery is a rechargeable battery that does not need recharging within one day. Although it is under development, the expectation of Developer 1 is that "This will still take something like three years." Other researchers share this expectation.

Another disadvantage of the battery is the size. The whole stimulator is implanted just beneath the skin, under the clavicle. It is not yet technologically possible to reduce the size of the battery, and thereby the stimulator. Researchers and developers I interviewed see this aspect as a bit more difficult, but as Developer 1 argues that in view of history, the battery size might be reduced in coming years. It is a technological challenge, but expected to be possible when we take a time span between three and

five years into account. I consider the currently used battery feasible to use for patients, but a reduced size and increased life expectancy would be beneficial. It seems plausible that the recharge abilities improve and that the battery size reduces, but development will take some time.

4.2.2 Minimize Side-Effects by Electrode Development

Aside from the battery, a patient has two electrodes implanted in the targeted brain region. The currently implanted electrodes have four contacts. However, research has been carried out in an attempt to use electrodes with many more contact points. Contarino et al. (2014) have performed a study with 32-contact electrodes in patients with Parkinson's Disease. This study shows that stimulation with a 32-contact electrode is safe with similar effects. There were no adverse events observed and the side effects were minimized (o.c.). Contarino et al. (2014) state that the results with the 32-contact electrodes are based on short-term results only and that long-term result is necessary for verification. More contacts can result in a change and enlargement of the exact brain area affected by stimulation. The four-contact electrode covers a surface of 6 mm^2 and a radius of 0.5 to 4 mm (o.c.). The 32-contact electrode has small contact points, used for directional steering of the stimulation. With directional steering, the spherical stimulation can change into a square in the case of four steering directions. The area for stimulation might be adjusted because of independent activation of several contacts (o.c.). Directional steering might not only be beneficial for patients with Parkinson's Disease, but for all patients with other diseases treated with DBS.

Researchers and developers I interviewed see this as a promising development. As explained during the interview with Researcher 1, "During stimulation, two different points of each electrode are activated." The points chosen for stimulation can change. This is a part of the application issues discussed in chapter five. Influential for the hardware is an increase of contacts of the electrodes. As claimed by Researcher 1, "Electrodes with a number of contacts up to 64 are currently under development." However, these electrodes are not in clinical use yet, so the effectiveness is unknown.The large area overlapped by the sphere of stimulation discussed as well during the interviews, and the researchers have the expectation that the electrodes with more contacts might be beneficial for targeted treatment of depression. In this case, literature and interviews concur with each other. Developer 1 states that "These developments will make it possible to direct the stimulation." The researchers included in the interviews had the same idea. Thus, the idea and the technology are there, but development and clinical research must continue to show the effectiveness and possibilities of directional steering.

Aside from directional steering, another proposal to improve the technological feasibility is non-continuous stimulation. Literature does not consider this aspect, but researchers and developers I interviewed believe that it would be beneficial for the patient if the brain is only stimulated when

necessary. Expected by Developer 1, but also mentioned by the other researchers, is a 'closed-loop system'. The electrode has to be able to detect the specific signals that cause a certain disorder–in this case, depression. A patient would not receive continuous stimulation, which could potentially reduce side effects. Developer 1 explains that "There are possibilities to build the closed-loop system and we have the ability to program everything we want." Aside from this programming, it is not yet feasible to detect and program when to act, due to the lack of knowledge about the brain. The closed-loop-system is not plausible for depression at the moment. It is probably earlier possible to incorporate a closed-loop system in patients with Parkinson's Disease, because of the lack of knowledge of the brain and the underlying mechanisms of depression is not sufficient. Although the development of this system depends on the knowledge of the disease, different actors consider it as a possibility. The closed-loop-system that can detect and act when necessary seems the best idea to focus on by developers; however, I think that it is not feasible the coming years.

4.3 Brain Region Selection in a Heterogenic Disease

As shown in the overview of ten different studies on DBS for depression analyzed by Galvez et al. (2015), clinical trials performed in a variety of brain regions possibly involved with the disorder. This seems a very important and difficult aspect as well for the technology as for the actual embedding of the treatment; there is no consensus about which brain region is involved with depression and most suitable for treatment. Depression is a heterogeneous disorder; thus, it is possible that different brain regions are involved. Research groups have their own hypotheses for a certain brain region for the treatment. I describe several hypotheses in this section, after which the difficulties with this aspect of brain region choice for the experiments, as well as for the treatment of depression, are discussed.

Another current discussion does include dynamical systems, selecting a spots to influence the dynamics instead of selecting a specific region for the implantation of electrodes. The Dynamical System Theory states that changes in psychopathology follow transitions in complex dynamical systems (Wicher, Wigman et al. 2015). Scheffer et al. (2009) argue that the underlying conditions of these systems influenced by variable factors make it difficult to disentangle the exact mechanism that is responsible for a change in the system. This theory states that nodes within a network can form a stable state in which the system does not change, even with a strong perturbation. However, when the system is in an unstable state, a small stressor is enough to cause a transition (o.c.). The difference for the application of DBS for depression is probably the determination of region for electrode implantation. The electrode will not be implanted in a specific brain region to stimulate that region, but a specific spot to stimulate a system. However, similar for the definition of brain regions involved, research to acquire more knowledge about the involved dynamical systems is necessary. Although this is a current discussion, this thesis will focus on the discussion about brain region selection.

4.3.1 Hypotheses by the Researchers

According to Bewernick et al. (2012, p. 1975), DBS research for the treatment of depression focuses primarily on three brain regions. The choice for these brain regions, driven by different hypotheses, includes the subgenual cingulate cortex (Cg25), the anterior limb of the capsula interna (ALIC), and the nucelas accumbens (NAcc). The hypothesis for Cg25 as a target for DBS is developed with the help of neuroimaging technologies, such as positron emission tomography (PET). The imaging leads to a suggestion to use the Cg25 region as target area for DBS as treatment for depression. "Depressed patients showed a unique pattern of elevated subgenual cingulate (Cg25) blood flow at pretreatment baseline" (Mayberg, Lozano et al. 2005, p. 655). The researchers have investigated the implantation of electrodes in this area in six patients with treatment-resistant depression. "A similar pattern of hyperactive Cg25 and hypoactive prefrontal cortex was seen in both DBS responders and non-responders" (o.c., p. 655). The difference in responders and non-responders was mainly seen in the magnitude of the prefrontal decreases. Only the responders show an area of hyperactivity in the medial frontal cortex (o.c.).

Malone et al. (2009) have selected ALIC because after DBS implantation patients with other indications seem less depressed, for example Obsessive Compulsive Disorder. They discuss that "The observations in Obsessive Compulsive Disorder, along with lesioning studies targeting the same cortico-basal circuity, led to our exploration of this target for the treatment" (o.c., p. 267). The researchers and physicians in the Netherlands have a similar hypothesis, as claimed by Malone et al. (2009). This leads to the hypothesis for using DBS in the NAcc to treat patients with depression. As Researcher 1 explains, "The idea is based on some theory, but other brain regions could be possible as well. However, the direct motivation resulted from the findings in other patient populations, which means that we are stimulating in the mood circuit." Other researchers base their hypotheses on theory. For example, Bewernick et al. (2010) choose to use the NAcc as the target of DBS for depression. "We aimed to ameliorate depression by modulating a brain area related to a specific symptom cluster. The NAcc was selected because of its central role in reward circuitry and its dysfunction regarding rewarding stimuli in patients with major depression" (o.c., p. 110). Overall, these three approaches differ in choice of reliable knowledge about depression, resulting in different criteria to select brain regions for DBS implantation.

4.3.2 Difficulties of Selecting a Suitable Brain Region

It is difficult to compare results of experiments due to the multitude of different hypotheses and identified targets. Altinay et al. (2015) argue that in all of the different clinical trials, there is not a single target region that appears to have superiority over another in terms of treatment effectiveness, the average ranges between 45 and 53 %. Current literature does not demonstrate any superiority of

one brain region over another for DBS treatment for depression, and it seems that the responsible circuits for this disorder might be modulated with the stimulation of different target regions (o.c.). Altinay et al. (2015) claim that the expectation that DBS will be a promising treatment for depression based on the belief that psychiatric disorders are caused by the dysfunction of a specific brain region. However, the data from different studies suggests that depression occurs due to the dysfunction of neuronal circuits, which involves several brain regions (o.c.). This is a problem when it comes to selecting the brain region most suitable for implantation.

Physicians state that patients with depression differ from each other, and this influences the results of experiments with DBS. Physician 3 claims that "The studies will not show univocal results, because the patient groups included in the research are too heterogeneous." This statement corresponds within the view of the other interviewees, and literature. As Physician 3 argues, "All physicians will emphasize that each patient is different, but they all have depression." It seems that an understanding of the underlying mechanisms can differ among patients as well. This is visible in the results with all treatment options for depression. Physician 3 elaborates, "One patient with depression will directly respond to a treatment with DBS and another will directly respond to ECT, but at the moment we are not sufficiently capable of distinguishing between the different patients."

An important question is whether you are able to distinguish between patients, and determine whether a patient is a suitable candidate for neuromodulation. Physician 2 claims that you have to determine the treatment for each patient individually, and in the case of neuromodulation, "The region for stimulation can differ from patient to patient." The other physicians agree with his claim. It is possible that neuroimaging could help to determine for each patient specific, but there is no available published literature on the results of neuroimaging after DBS treatment. Other interviewees, such as the researchers, agree that it is difficult because of the heterogeneity. However, they do not argue in detail about this difficulty. Concluding, it does not currently seem plausible to determine beforehand which patient would be suitable for a DBS treatment, or which brain region should be selected for treatment, yet it seems necessary to determine this for each patient. This implies that the research should continue to acquire more knowledge about the effects of DBS on different brain regions before it will become possible to use DBS as a regulated treatment in the psychiatric care.

4.4 DBS Seems Technologically Feasible

The goal of this chapter was to evaluate the plausibility of expectations about the technological feasibility of DBS for depression. I analyzed the capabilities of the technology with the current use and developments. I conclude from literature and interviews that it seems technologically feasible to use this technology for patients with depression as used in clinical trials. The technology has been developed and improved to treat patients with different indications. DBS tested in different settings, making comparison difficult, but results seem positive. Aside from a general comparison of

experiments, there are some expectations about the technological improvements requiring further discussion and analysis. The components of the hardware of DBS are rapidly evolving. The main expectations mentioned in this chapter are a smaller battery with better recharge abilities and electrodes with multiple contacts and detect ability.

From the interviews I expect that it is plausible that the battery life will improve and that the size will reduce, but the latter needs a bit more effort. Another plausible expectation is the development of more contact electrodes (from 4- to 64-contacts). The electrodes are already developed and some used in clinical trials. Although this is currently only for Parkinson's Disease, it is shown to be technological feasible. The effects of these electrodes with the treatment of patients with depression are unknown and require more research. Another future oriented expectation of electrode capabilities is a closed-loop-system. The idea raised by researchers and developers during the interviews is to detect and act only when necessary, reducing side effects. I consider this not feasible the coming years. This means that some of the side effects will remain a problem for the time being, but it is possible that the use of directional steering can reduce these as well. The idea that DBS might be a treatment for mental disorders used in the military sector as well as the medical sector as argued by DARPA seems plausible with the current hardware and further research to investigate new technological parts.

Although the expectation that more contact electrodes used for directional steering and a more personalized treatment is plausible, a problem remains the limited knowledge about brain regions. The bottom line is the difference in target regions used in clinical trials due to the heterogenic clinical picture of depression and unequivocal knowledge. The hypotheses for experiments have various criteria, resulting in a variety of brain regions used in research. These different regions lead to incomparable results, making it difficult to base conclusions. Overall, the expectation that one brain region will be the target for implantation seems implausible. The disorder is heterogeneous and it is possible that when DBS will be proven beneficial for (some) patients, the brain region suitable for implantation differs from patient to patient. For the time being, there is limited knowledge about the brain regions and an absence of tools to select for each patient. That it might be beneficial for some patients is proven, but the general expectation that DBS for depression is beneficial seems implausible. The expectation raised by the DARPA researchers is to use this technology for treatment and for prevention of depression or mood enhancement, however, this seems not plausible due to the limited knowledge about brain regions or maybe dynamical systems involved with the disorder. Therefore, I will focus on the possibility of treatment in the following chapters.

5. Social Usability

There are many options to treat a patient with depression, ranging from talking to ECT. DBS as a treatment for depression is in the experimental phase, and not accepted or incorporated within current psychiatric care. However, the idea to embed DBS in the psychiatric care in the near future is already widespread in literature. Moss (2013, p. 1) argues, "Deep Brain Stimulation is emerging as a viable option for treatment-resistant depression." From this argument, I would consider that the technology is possible in the current health care. However, it is still experimental and not clear whether the expectations are plausible. Different studies have been performed to show the benefits of DBS in psychiatric care. Solomon (2014, p. 6) argues that "The most radical breakthrough is deep brain stimulation (…) absolutely astonishing results with people who failed every other kind of treatment." Will DBS become a radical breakthrough in the psychiatric practices or not?

Reflection on the social usability, as proposed by Lucivero et al. (2011), is the next step in assessing the plausibility of expectations. Social usability is included to discuss whether possible technological expectations might imply social conditions that are impossible (o.c., p. 135). It might be possible for example to develop a smaller battery, but recharging within less than a day implies hard condition for the patient. It is possible to create a detailed image of what use beyond the laboratory might look like, building on relevant current practices and envisioned new practice (o.c.). Lucivero et al. (2011) argue that actors can share opinions and ideas about possible aspects of use that need to change, become prevented, or encouraged. A useful tool is a 'thick description', of which points out the social conditions that are implicit in the expectations, to imagine the new technology in the social context (o.c.). For example, practices of psychiatrists might change with the introduction of DBS including a surgery. These changing practices require evaluation before embedding in psychiatric care.

This chapter will discuss the context of use in current care, as well as possible care with the embedding of DBS. I will analyze both contexts, with the use of a script of current care and a script of DBS for depression based on literature and information gained during the interviews. I use the scripts to determine which aspects or expectations seem too speculative for further discussion. 'Is it plausible for DBS to become embedded in the care of patients with depression?' I start with a description of script. The definition of script and the possibilities for analysis might help to make a thick description of the current situation in psychiatric care, and a script of the envisioned practices of DBS to treat depression. Both scripts are used to construct scenarios for patients and other actors involved with DBS in the health care system. The second part of this chapter includes some difficult issues for embedding in the case of DBS for depression, such as determination of stimulation settings and patient selection.

5.1 Analyzing the Script of Deep Brain Stimulation

Akrich (1992) has defined the term 'script' for the analysis of the relationship between users and technologies. She compares it with a film script. "Technical objects define a framework of action together with the actors and the space in which they are supposed to act" (o.c., p. 208). With the use of script, a study focuses on the definition of the users' specific tastes, competences, motives, aspirations, political prejudices, and other perspectives. This helps to create a probable vision of the world in the technical content of a new object (o.c.). Akrich (1992) argues that the designer of a technology has to imagine the probable use, and the probable users, of the new technology. The designer applies the imagined scenario in the decision making process of the use of the artifact and defines what should be left for initiatives of the users (o.c., p. 216). According to Akrich (1992), the designer puts the idea who will become the user of a device in the initial script. Different users can interpret new technologies in various ways (Troja 2009). On one hand, a user can have a similar vision compared to the designer. The script can become the main element for interpreting the actions of a user with the object; these users are the projected users (Akrich 1992, p. 216). On the other hand, a user might interact with the device in an unpredicted way. The user does not follow the script and becomes a designer in a certain way. He discovers new practices and applications to use the device (o.c.). As Akrich (1992) puts it, these users help themselves to achieve their own goals and program of action, the intended script might differ from the initial script by use in unintended ways.

Innovation studies show the simultaneous technical and social shaping of innovations. De Laat (1996) argues that proposals for visions, and assumptions of the innovation in the future world, are more or less shared. The scripts made by project managers or designers and shared by people concerned with use (o.c.). Jolivet et al. (2003) argue that scripts focus on factors that count and point to relevant transformations that need to be realized with the introduction and use of a new technology. Different actors need to learn about DBS, how they can and need to use it (o.c.). It is important to analyze this before embedding, because designers have a responsibility to identify required changes and start to build the route to follow (o.c.). For the script of DBS for depression, it is possible to apply the concept of roles to analyze all different actors, such as their contributions and interactions with the use of a technology (De Laat 2006). As Goodyear et al. (2014) claim, social networks are composed of nodes or actors and the connections between them. Actors might have their own goals, ambitions and actions, but connected with the other actors to form an overall goal, to have an effective treatment for patients with treatment-resistant depression, in the case of this thesis. A technology can have very specific implications for the roles of different actors involved with the technology; for example, the embedding of DBS within psychiatric care will introduce surgery to the working domain of a psychiatrist. In addition to the possible new actions and practices, Parthasarathy (2012, p. 20-21) argues that a role presupposes a set of rights, responsibilities, and relationships. Consider the patient and the psychiatrist; there is a presupposed relationship between them, which is critical for the

treatment of that patient. The psychiatrist is responsible for listening to the patient and providing care, and the patient is responsible for showing up at appointments. This relationship, with its responsibilities, will not change after embedding DBS in psychiatric care of depression.

5.1.1 The Script of Psychiatric Care of Patients with Depression

The concept of script can be used to investigate the influence of a new technology. Before I discuss a possible script of DBS for depression, I analyze the current psychiatric care practices, with the use of the protocol for diagnosis and treatment of depression as described in chapter two and the interviews, as a starting point to build a script for a new technology. Different actors are involved with the different therapies for patients with depression. First, the general practitioner (GP) of a patient coordinates the (first) care. When the GP evaluates the treatment and it is determined that the treatment needs expansion with psycho- or pharmacotherapy, more actors become involved. Psychotherapy includes treatment realized by a psychologist, psychiatrist, or another therapist. Pharmacotherapy includes the pharmacological industry, the laboratory, and the pharmacist. A GP can forward a patient to a psychiatrist if and when the patient does not respond to any treatment that the GP can provide. The psychiatrist will evaluate the patient and probably recommend different treatments based on that person's specific needs. He becomes the coordinator of the treatment process. A psychiatrist can discuss with the patient to start ECT, introducing other professionals such as an anesthesiologist and nursery personnel at the psychiatric ward of the hospital.

Overall, the current practice of the treatment of patients with depression, and all different steps in this protocol, will involve different actors with specific roles, responsibilities, and competences. I have compiled an overview of the different therapies with the roles responsibilities, actions, and competences (see Table 4). The description of the basic treatments, psycho- and pharmacotherapy, is rather short. The analysis of the ECT script is more extensive and therefore probably most comparable to the possible script of DBS for depression.

Table 4. An overview of the different therapies in the protocol of the treatment of depression. The involved actors with their roles, responsibilities, and competences are included for each treatment.

Therapy	**Actors**	**Roles/responsibilities**	**Competences**
First basic treatments	Patient	Go to the GP for a consult and return for each evaluation. Give the GP information about the depressive state. Perform the given therapy.	Recognize that he has symptoms of depression. The ability to visit a GP. The motivation to perform self-therapy. Understand how to do the therapy. Time and opportunity to perform the therapy, for example the ability to read.
	GP	See the patient and diagnose. Determine which therapy could be beneficial.	Understand and recognize depression and the symptoms. Understand the outcome of depression

		Evaluate the treatment and determine next steps.	rating scales and know whether or not the therapy is helpful. Have knowledge about self-therapy possibilities.
Psychotherapy	Patient	See different therapists and return for all appointments. Adhere to the given treatment.	Motivation and opportunity to go to appointments. The ability to speak. Understand why he should talk about the situation. Trust the therapist.
	GP/psychiatrist	Keep track of the situation. Evaluate the treatment and determine next steps.	Have contact with the other therapists. Understand and evaluate the therapy performed by others.
	Other therapist	See the patient and talk with him. Analyze and evaluate the conversations and find the need for the next consults. Give the suitable therapy.	Understand the patient's situation. Keep track of the previous sessions. Gain trust of the patient. Have the ability to listen to and speak with patients.
Pharmacotherapy	Patient	Go to the pharmacist to obtain the drugs. Take the given drugs. Motivation to adhere to the treatment.	The ability to swallow or competence in other ways to take drugs. The opportunity, and means to get and pay for the drugs. The ability to remember to take drugs.
	GP/psychiatrist	Determine which drug will be the best to take for each patient. Evaluate and determine next treatment steps.	Understand the different mechanisms and effects of the different drugs. The ability to change drugs when necessary. Keep track of the situation of the patient.
	Pharmacist	Give the correct drug. Explain effects and risks to the patient. Control the different drugs taken by the patient.	Have knowledge about all different drugs, the (side-) effects, risks, and influence of other drugs. Ability to control and check the total drug intake of the patient.
	Laboratory	Test the drugs and the effects for the patients.	The ability to understand the results of experiments.
	Pharmacological industry	Investigate the current market and research the drugs for depression. Development of new drugs.	Know the needs for new drugs and respond to that. Guarantee safety and efficacy.
ECT	Patient	Accept the treatment and adhere to appointments for ECT sessions. Arrive at the hospital for every session. Take place in the bed in which the treatment will be given. Relax before the procedure starts and the muscle relaxation medication is given. Awake after the insult.	No sufficient response on other treatments. Understand and give informed consent. Be awake before therapy starts. Needs an extremity for the measurement of the insult. Indicate his conditions before and after an ECT session. The time and opportunity to go to the hospital for each session. Understand the possible side effects and know which are undesirable. The opportunity to go to someone when something happens outside the hospital.
	Psychiatrist	Coordinate the care of the	Have an understanding and overview of

		patient. Inform the patient about the treatment and its risks and benefits. Check the different settings before and during ECT. Perform the treatment correctly and evaluate the outcome.	the treatment history of the patient. Knowledge about the ECT procedure. Have the correct devices available to perform the procedure. Understand the influence and outcome of the ECT. Have contact with the others involved (anesthesiologist and nursing personnel). Have a computer to check settings beforehand and log the procedure and insult afterwards.
	Anesthesiologist	Give and check for the correct medication. Assist during the procedure. Watch over the physical conditions of the patient.	Knowledge about the influences of ECT on the conditions of the patient and how to respond on undesirable changes. Have the opportunity to call someone in case of emergency. Know how to wake the patient and respond on possible side effects. Have monitors to watch over the patient.
	Nursing personnel	Take care of the patient. Watch over the conditions of the patient after ECT. Have contact with psychiatrist.	Time to watch over the patient. Ability to take care and know what needs to be done for each patient. Understand the condition of the patient and the influence of ECT. Evaluate and know when the patient can leave the hospital.

5.1.2 Script of Deep Brain Stimulation for Depression

DBS is not embedded in current psychiatric practices; thus, the script of DBS for depression is not clear, but can be based on the experimental set-up by the research groups. Altinay et al. (2015) discuss that a main issue remains to know when and how to use DBS. They claim that "The use of medication and peripheral neurostimulation should always precede DBS for psychiatric disorders until research indicates otherwise" (o.c., p. 348). All interviewees agree and suggest DBS as a treatment option at the end of the protocol for patients with treatment-resistant depression. However, Developer 1 argues that it is possible for this to change over time.

I start by defining the involved actors in the therapy process, after which I investigate the goals and ambitions, roles, responsibilities, and competences of the actors. I use the experimental set-up of the research in the Netherlands to develop the script. The ultimate goal for the patient is to be 'cured' of depression. The ambition to diminish the depressed feelings, when all other treatment options fail, might result in an acceptance of a more radical treatment like DBS. Before this can become an option, the patient needs to have undergone different pharmacological and psychotherapies, and several ECT sessions. This is a long process, and the patient needs to be capable of taking all steps and adhering to treatments during this time, I describe a possible scenario of the patient in 5.1.3.1.

The goal of the neurosurgeon is to implant the electrodes and stimulators correctly in the predefined brain region. Physician 3 argues that defining the brain region should be a multidisciplinary

process. All actors involved with the treatment should be included in the decision-making procedure. Although the brain region for implantation is predefined in current clinical trials, this could potentially change over time. I will discuss the possible influence of brain region selection on the situation in care in the reflection part of this thesis. The neurosurgeon has the ambition to eliminate side effects, and he takes every possible step before and during surgery to determine the correct procedure. The goal of all physicians is to 'cure' their patients. The psychiatrist is involved in the treatment as well, especially before and after the surgery. His goal is to give the patient a suitable treatment that helps them overcome the depressed feelings. The ambition to find suitable settings for stimulation underlines his actions to change and/or stop the stimulation when necessary. He will evaluate the effect on the patient, and after a long process of changing settings, the psychiatrist can compare the different settings to find the most desirable. He makes the stimulation patient-specific and more personalized.

There are other actors involved making the treatment possible, such as the developers of the technology and the health care providers. The goal of the developers is to create a technology with the highest quality. In addition to a high performance, the technology should be desirable to the different actors that potentially use the technology. The developers have the ambition to research and experiment with the technology, and acquire results to show effectiveness. They might improve the technology and search for research groups to study the use of the technology. DBS for depression is in the experimental phase, thus the researchers are involved as well. Their goal is to show the effectiveness of DBS for depression. In the effort to do this, they perform different experiments and analyze the results. I have included the researchers because of the possibility of them staying involved after embedding. Probably more research remains necessary to optimize the treatment. Research can have consequences and can introduce changes in the script. It is, for example, possible that researchers suggest a different use of the technology. It is also possible for a certain device not to be suitable for use in a clinical setting. In that case, developers can change the design of the device.

Table 5. An overview of the actors involved in the script of DBS for patients with depression. Each actor is included with a description of his goal and/or ambitions, roles and responsibilities, and the required competences.

Actor	**Goal/ambitions**	**Roles/responsibilities**	**Competences**
Patient	To diminish or overcome the depressive feelings.	Undergo psycho- and pharmacological-therapies, and several ECT session. Accept DBS and give informed consent. Come to the hospital for the surgery. Adhere to all consults to evaluate and change the stimulation settings. Live with the DBS. Recharge the battery approximately every day (in	The ability to live with the depression, undergo all previous treatments, and accept a surgery. The ability to give informed consent, mental competence. Understand what should happen and know or recognize when undesirable side effect occur. Know what to do and/or where to go when side effects occur. Have the physical conditions to undergo the surgery. Motivation to come back to the

		case of a rechargeable battery).	hospital for all appointments, even when the situation is desirable. Ability to recognize and report all effects.
Psychiatrist	To help/'cure' the patient by finding the best therapy	Give correct information about the whole procedure, risks, effects, et cetera. Give the patient the best possible treatment. Change the settings for stimulation and evaluate the state of depression (HAM-D) during each consult. Determine the best stimulation settings for each individual patient. Stop treatment when necessary, in case of highly undesirable effects or when the patient wants to stop.	Understand the working mechanisms of DBS. The ability to understand the situation of the patient. Knowledge about the different options and influences of stimulation settings. Know what to do and when. Recognize the effects the treatment has on the patient. Ability to interpret the observed effects and translate that to the stimulation settings. Ability to motivate the patient to report the effects of stimulation. Have devices available to adjust the settings.
Neurosurgeon	To perform a correct implantation of the electrodes and stimulator.	Prepare the treatment. Determine procedure and brain area for implantation, when not predefined. Perform the surgery as prepared. Watch over the condition of the patient during implantation and evaluate first effects. Overcome side effect of the implantation and obtain the best results possible.	The capability and experience to perform a DBS surgery. Understand the technology and knowledge how to implant electrodes, wires, and stimulator. Know the situation of the patient and use this to determine the procedure. Have the devices available for implantation and first stimulation. Know which effects are desired and which are undesirable that could be overcome during surgery.
Nursing personnel	Take care of the patient.	Give care when required after surgery. Take time to watch over the conditions of the patient. Have contact with the physicians about the situation of the patient.	Time to watch over the patient. Understand the condition of the patient and the influence of DBS. Ability to acquire knowledge about DBS, depression, and the desirable as well as undesirable effects of DBS on the patients. Ability to recognize effects which need immediate action. Know which care is necessary for each patient. Recognize when the patient can leave the hospital and evaluate this with physicians.
Developers	Develop and improve the technology.	Research and experiment with the technologies and acquire results to show the effectiveness. Improve the current technology. Search and contact with groups which will use the new technologies for research.	Understand the health care system, understand the need of DBS in a specific branch, the psychiatric domain. Have the (technological) knowledge to improve the current devices. The means to improve or develop new technologies/devices. The time, work space and opportunity to develop or improve.

			Understand the outcome of research and have the ability to interpret these reports and translate to development.
Researchers	To show the effectiveness of DBS for depression	Make a set-up and guidelines for the research. Select the patients and make guidelines with inclusion and exclusion criteria for this selection. Perform all experiments according to the set-up and guidelines. Analyze the results and possibly write reports. Probably show the results to the scientific or wider public. Make recommendations for further research.	Knowledge about the mechanisms of the technology and depression to set-up a research. Understand the health care system and the possible need for a new technology. The ability and means to perform research with the use of DBS devices. Cooperation with a hospital to perform the experiments and ability to contact patients. Understand the possible effects ad side effects DBS can have on the patients with depression. The ability to recognize effects and report in a way that it is understandable for others.

5.1.3 Scenarios of a Possible Future for DBS

I consider the previously presented script based on experimental settings as plausible for the embedding of DBS in psychiatric care. First, I use this script to analyze a possible scenario for a patient diagnosed with depression. Possible scenarios about expected advantageous technologies additional to the treatment protocol follow this.

5.1.3.1 The Process for the Patient

Researcher 1 discusses the inclusion and exclusion criteria in the research performed in the Netherlands. A patient is only qualified for DBS after psychotherapy, drugs, and several ECT treatments. The patient undergoes these treatments for at least one or two years before DBS becomes an option. More specifically, previous treatment has to include a variety of drugs, including SSRI's or SNRI's, lithium, and a monoamide oxidase inhibitor, and a series of twelve ECTs. As Researcher 1 claims, "These patients are exceptionally treatment-resistant." They should not suffer from bipolar depression, and should not have manic episodes, psychosis or schizophrenia.

When the psychiatrist gives his patient the option to choose for DBS, the patient will be informed. The patient should understand the information about the whole procedure, surgery, the time to determine desirable settings, the risks, benefits, and all effects. He needs to assimilate all the information and be mentally competent to make the decision about the DBS surgery and follow-up. I discuss this aspect in detail in the next chapter. When the patient gives his informed consent and accepts the treatment, the physicians will start preparing the procedure. Due to the expertise necessary for this surgery and treatment, DBS will not initially be available in all hospitals, but only in a selected group; for example, hospitals already involved in the experiments. This is beneficial for the expertise of the physicians because they treat multiple patients a year, improving their capabilities and

experiences. This means that some patients would need to travel for the surgery as well as the follow-up.

The patient needs to stay awake during the whole procedure to answer several questions or perform some simple tasks during the surgery. Patients have to repeat a sentence or wink an eye, and the physicians evaluate the reaction of the patient. This will give them an impression about the first response on the electrodes and stimulation. After surgery, the patient has to recover. He is nursed at the hospital and can return to home when possible. In the following period, the patient will make appointments and return to the hospital for evaluation and adjustment of the stimulation. The patient needs to describe his situation, the effects the stimulation has, and the current state of the possible depressed feelings. This means that he needs to both recognize the changing effects and feelings and have the ability to report this to his psychiatrist. The returns to the hospital will take place approximately one week after each change of settings. During this period, the patient has to be able to adhere to the treatment and return to the hospital for every appointment. This is a long process of one to two years, comparable to the current experimental set-up.

If and when the patients respond well to the treatment, do not have the depressed feelings anymore or are less depressed, the stimulation continues. During this period of continued stimulation, the patient will have periodic appointments with his psychiatrist; probably every one or two months. The patient and his relatives needs to be aware of undesirable effects and return of the depression. A return of the depression could be the result of a dead battery, most likely occurring between eight and thirteen months after the start of the stimulation. In the case of a rechargeable battery, used in the current situation, the patient needs to recharge every day for approximately one hour.

When a patient does not respond to the treatment or does not wish to continue with the therapy, the physicians stop the stimulation and remove the electrodes. The patient remains under supervision of the psychiatrist, who has to evaluate the approach to handle the depression. Researcher 2 argues that the difficulty with this treatment is that it seems actually the last chance for the patients. He discusses that “These patients have little hope and DBS can give them any perspective. In general, the patients would prefer euthanasia when they do not respond to the treatment.” Other researchers and psychiatrists I have interviewed agree with this idea, but argue that we should not actively support euthanasia. The procedure of euthanasia can only start with a request by the patient, otherwise the patient might consider the option of euthanasia in case of non-response.

5.1.3.2 Future Possible Changes in the Scenarios

It is possible that other embedding scenarios of DBS in the psychiatric care evolve if and when the technology is shown to be effective and beneficial. The previously described scenario is based on the current experimental setting. However, the treatment is under research for the coming years, and it is possible for this research to show that inclusion of other steps, such as imaging, could be beneficial for

the outcome of the treatment. This would change the procedure and the roles of included actors. The scenario prior to the surgery could change with the inclusion of MRI or a different imaging technology. A scenario with imaging includes that each patient will undergo a scan, and the results will determine whether a patient is qualified for the treatment. This extra step before surgery introduces a slightly different procedure and invites new actors. The patient will come to the hospital for the MRI. Radiologists will perform the MRI measurement when the patient does not have any contra-indication, such as metal or electrical stimulators inside the body and is not scared to undergo this scan. With MRI the radiologist might become included. His goal might be to obtain correct images useful for other physicians to specify the area for implantation. The radiologist will likely be included in the multidisciplinary process to plan the procedure for surgery. After this planning, the same process of surgery and follow-up consults to evaluate the conditions and change stimulation settings will follow. In this possible scenario I imagine the only change is the inclusion of another actor and an imaging technology included in the decision making process.

Another example of how the scenario above might evolve is the inclusion of biomarker detection. A possible extra step, suggested by Galvez et al. (2015), is to analyze responses of several biomarkers before and after stimulation, such as pro-inflammatory cytokines and oxidative stress levels. Biomarkers will help to gain understanding of the underlying pathophysiology of depression, and the influence on these biomarkers after the electrical stimulation can be observed (o.c.). Glavez et al. (2015) suggest that the knowledge of important biomarkers is useful to determine the best application for each patient. The only interviewee that mentioned biomarkers was Developer 1. He argues that "One of the problems with determination of a suitable treatment is the heterogeneity of depression, but another problem is the absence of known biomarkers." The set-up of a clinical trial is difficult, because there is insufficient knowledge about biomarkers. Research on biomarkers would be beneficial for expanding knowledge about the underlying processes during DBS treatment. When it becomes beneficial to use biomarkers to determine the outcome of treatments, the analysis of specific biomarkers might be included in the procedure. It is hard to create a scenario of this very speculative method, because it is, for example, unknown whether the laboratory needs a biopsy or a blood sample to measure the biomarker. The function of biomarkers is unknown and it is therefore difficult to define the different steps actors have to take during this process. Currently, the measurement of biomarkers is just an idea. The development could take several directions, including different actors.

The following is a speculative scenario that includes the use of biomarkers. The patient undergoes different therapies before the psychiatrist might measure biomarkers, however, it is possible to measure biomarkers in every stage of the treatment. When it is clear that a patient has a biomarker that indicates they are a good candidate for DBS treatment, the physicians potentially treat the patient in an earlier stage. Probably the biomarkers have to be analysed in the laboratory and the laboratory

technician interprets these results. The psychiatrist will coordinate the steps after a multidisciplinary consultation to determine the procedure that is to follow. If and when knowledge of biomarkers is determined to be beneficial after surgery as well, a similar procedure to define biomarkers and analyse the results will also be performed post-surgery. The patient has to come to the hospital for an evaluation and a change of stimulation settings as well as for a biopsy or blood sample. The results can have an influence on the follow-up of the treatment. It is necessary for the patient to return to the hospital several times for the measurement of biomarkers; this will make the whole procedure more complicated, but it can have a beneficial influence on the outcome of the treatment. It is also possible to exclude patients who do not present a certain biomarker or present a different biomarker. This might overcome unsuccessful brain surgeries. However, acquiring more knowledge about biomarkers is necessary before embedding as a step during the treatment or used to include or exclude patients. It is plausible that future research includes biomarkers, but for now it seems implausible to state that it might be beneficial for the treatment.

MRI as well as biomarkers have to show beneficence for the treatment before I consider it plausible to include them in the embedding of DBS as a treatment for depression. In addition to the future possible scenarios, some issues can reduce the plausibility to introduce DBS in psychiatric care. In the remaining part of this chapter, I will discuss some of the difficulties, argued on in literature and during the interviews, which are seemingly important for the embedding of DBS for depression.

5.2 Difficult User Issues with the Embedding of DBS

This section includes the arguments shared by the different interviewees. These issues were already incorporated in the previously described scenarios, and shown to be possible to embed in a way comparable to clinical trials. However, some issues are actually more difficult and influential for the embedding of DBS for depression. I start with a discussion about the process used to determine the optimal settings for electrical stimulation, continue with the difficulty of patient selection, and end with the influence of insurance companies on the possibility of embedding.

5.2.1 The Trial an Error of Searching for Optimal Stimulation Settings

It is a long and difficult process to define the stimulation settings with the greatest effect on a patient. In literature Mayberg et al. (2005, p. 652) state that the stimulation settings that were found to be free of adverse effects became the basis for the selected stimulation settings. Overt adverse effects, such as lightheadedness and psychomotor slowing, only observed with the use of a high voltage, and in most cases seen at the superior contact. “The mean stimulation parameters used in this group at 6 months were 4.0 Volts, 60 µs pulse widths, at a frequency of 130 Hz” (o.c., p. 653). The final contact selection and stimulation parameters tested over five days after surgery, with a follow-up period lasting up to 6

months (o.c.). Bewernick et al. (2012) argue that the stimulation parameters vary between patients. "Most patients were stimulated between 5 and 8 V, at 90 µs, 130 Hz, monopolar" (o.c., p. 1978). They also change the settings in individual patients when side effects occur, or when there are unsatisfying antidepressant responses. First, the amplitude followed by the pulse width, the selection of poles, and then frequency changes. Responders had minor setting adjustments 13 months after surgery, and non-responders on average had more parameter changes still at 17 months after surgery (o.c.).

Current literature shows that there is a mean stimulation setting found with each experiment, the voltage of which differs between research groups. However, as Lozano et al. (2008, p. 466) argue, the stimulation parameters to reach desired effects vary between patients. There is a variety in electrode contacts as well as electrical stimulation settings chosen to reach the optimal antidepressant response for each individual (o.c.). Another important detail for the research is the time to evaluate the antidepressant response of a certain setting. It is possible for the response to be progressive over time, or for an initial large effect followed by decay (o.c.). Most research groups control settings approximately 7 days after stimulation. Schlaepfer et al. (2013) argue that they want to have a reduction in depressive symptoms of >50% for 7 days after onset of stimulation. The simulation continues after reaching this reduction (o.c.).

The descriptions of stimulation settings in literature are congruent with the descriptions given during the interviews. Researcher 2 explains three different elements important during the analysis of stimulation: voltage, frequency, and pulse width. As Researcher 1 explains, "There is an idea behind the settings of stimulation." He does not discuss the idea, but he explains that out of the three different elements, the pulse width and frequency are stable during the experiments. Previous research has shown that the stimulation needs 100 Hz, pulses per second, or higher. He explained that they use 130 Hz in the treatment; this is similar to the mean stimulation setting of research by Mayberg et al. (2005) and Bewernick et al. (2012). Researcher 1 explains that the voltage and the contacts that are activated change during the experiments and psychiatrists evaluate every change after at least one week. Equivalent with literature, Researcher 1 explains that they also test different settings for at least one week to know the effect. "This is necessary because symptoms of depression are not acutely measurable and you need to test whether the effect prolongs." Physician 2 argues that, "We need to understand the changes before we are able to influence." DBS might give us the ability to observe and analyse the exact changes and evaluate its influence on depression. It is possible to analyse the disorder and the responses observed when stopping the simulation or changing parameters. However, as Researcher 1 explains, "It is difficult to measure symptoms of fear or depression in an acute phase, and it does not mean that the effect is prolonged when the disorder directly ameliorates."

A disadvantage due to the unknown optimal settings for the treatment of depression with DBS is that the search for the optimal settings is a long process. As Researcher 1 explains, the whole period

to adjust the settings will take approximately one year. Although this is disadvantageous, and certain settings can result in undesirable side effects, it is also possible to stop or change the stimulation at any moment. Developer 1 sees this as a smart innovation, an advantage, and a possible way to overcome side effects. Researcher 2 explains that "A certain brain area is switched off during stimulation; however, we can stop the stimulation when this leads to undesired consequences. The brain area will work like it did before stimulation." In addition to the advantage of overcoming side effects, Physician 2 thinks that DBS will have fewer side effects than medication due to the specificity of the treatment. "DBS makes it possible to treat a certain area where medication influences a whole system," he states. The trial and error phase to search for desirable stimulation parameters that are suitable for an individual patient remains part of practice. It would be beneficial for the patients when there is a mean stimulation setting determined that be a starting point for the stimulation and taken in the scenarios previously presented. However, this is not plausible at the moment, and the very long trial and error phase described in the scenario remains the only option for the time being.

5.2.2 Select Patients Based on Well Defined Criteria

The patient selection is the main issue concerning the embedding of this technology mentioned in literature as well as during the interviews. Studies to investigate DBS for depression construct several inclusion and exclusion criteria. For example, the research performed by Lozano et al. (2012) includes men and (non-pregnant) women with an age of 30-60 years diagnosed with nonpsychotic major depressive disorder. The onset of the first episode should be before 35 years. The patient need to suffer from chronic depression with documented resistance to at least four depression treatments in a lifetime and documented resistance in the current episode to a minimum of three adequate depression treatments and at least six ECT sessions. People with psychosis, past intracranial neurosurgery, or depressive episodes with atypical symptoms were excluded from the study (o.c., p. 317). In the first study by Mayberg et al. (2005, p. 657), "Patients were selected for surgery because they were resistant to all available therapeutic options." The inclusion and exclusion criteria used by other research groups, for example Malone et al. (2009, p. 268) are similar, regarding the documented resistance and the contraindications.

The issue of patient selection was considered by all interviewees. Physician 2 asks, "Depression is heterogeneous, so how can we know whether DBS is providential for one patient and not another? Who will receive treatment and who does not?" He argues that it is very hard to define for which patients DBS would be beneficial. Congruent with the literature, all interviewees agree that only the severely treatment-resistant depressive patients should be treated with DBS (at this moment). Researcher 1 explains that "There is no actual definition for treatment-resistant depression, but we

have defined it as patients treated with two different types of SSRIs and SNRIs, one TCA (with lithium), one mao-inhibitor, and a series of 12 ECT treatments." Next to inclusion and exclusion criteria to select the extreme treatment-resistance, the patient should also understand the treatment and understand that there is no guarantee of success. Additional exclusion criteria are, for example, dementia, schizophrenia, bipolar depression and/or psychosis. This is comparable to inclusion and exclusion criteria in literature.

For future scenarios, Researcher 1 argues that "It would be the same patient group and the less severe depressive patient would not be treated with DBS." He thinks that it would not be possible to extend the indication for treatment with DBS because it is not achievable to incorporate it into the current health care system, and it would become too expensive. Other actors I have interviewed share his view. Physician 3 agrees that the selection could be a problem at the moment; however, when a multidisciplinary team of psychiatrists, neurosurgeons, and all others involved agree that a patient is eligible for a DBS treatment, this patient should get the option to choose DBS. This view includes the acceptance of DBS at an earlier stage in the protocol, for example similar to ECT. Physician 1 does not agree with this. He argues that ECT is effective and beneficial and therefore "DBS should take place definitely after ECT." He states that even when DBS is beneficial, the costs-benefit analysis will probably show that ECT should be performed before DBS.

For the previously discussed scenarios, it is currently more plausible that DBS will be included at the end of the protocol. The inclusion and exclusion criteria, similar to the current experimental phase, should be included in the scenarios. When DBS shows to be beneficial, it is plausible to apply these criteria for patient selection. In view of the scenario, for example biomarkers inclusion, it can become plausible that a multidisciplinary consult concludes to consider DBS at an earlier stage in the treatment of patient with depression. Alternatively, they conclude to exclude certain patients from DBS, for example those who do not present a certain level of cytokines.

5.2.3 Incorporation of DBS in the Insurance

One of the primary issues for actual embedding of DBS as a treatment of depression is the insurance. A treatment needs incorporation into the insurance system. Health care providers 1 and 2 explain that insurance bases on science and practices in care. There are guidelines before a treatment becomes insured. A new treatment needs to be evidence-based effective. The most important experiments taken into account are randomized controlled trials and systematic reviews by different research groups. Health care provider 2 explains that the two questions asked to evaluate a treatment for coverage are, 'Is it effective?' and 'Is there something else inducing the same?' Overall, the most important thing is to create a balance between the side effects and the harmful and non-harmful effects. "There needs to be a medical necessity and the intervention needs to show effectiveness," explains Health care

provider 1. However, as Health care provider 2 argues, “This can be difficult with DBS for depression, because it will take a long time before you know the actual results.”

Physician 1 argues that you need to be very critical, because “When DBS is insured for too many patients and the procedure shows low efficacy, the health care sector will bite its own tail”. Thus, acceptance for too many patients can have a negative result on the total positive outcome. Health care provider 1 stresses this as well, because results of the treatment will go back to the insurance company and they can reconsider the incorporation of DBS within the insurance.

Literature does not outline the insurance and possible implications that could prevent embedding of DBS for depression. Different countries have a variety of regulations in their insurance systems, but I will focus on the possibility of insurance coverage in the Netherlands. According to the interviews with the health care providers, the policy to embed a technology like DBS for depression requires care. However, it seems plausible to embed DBS for treatment-resistant depression in the health care system and insured after further research with more evidence-based results. Although the previously created scenarios will not change, the insurance companies can apply certain rules to the insurance coverage and these rules require to be included in the scenarios, such as the hospitals for treatment and the inclusion or exclusion criteria for patient selection. Beforehand evaluating these aspects is useful to include it in the design and embedding scenario of the technology.

5.3 It Might Become Plausible to Embed DBS for depression

Literature and interviewees present DBS as a possible solution for treatment-resistant depression. However, questions concerning patient selection require further research before embedding of the technology seems plausible. The goal of this chapter was to analyze the current health care practice of depression, and possible scenarios for inclusion of DBS in psychiatric care of depression. Based on the current technological possibilities and the current experimental set-up, I suggest that it is plausible to embed DBS in the care of patients with treatment-resistant depression. However, there are several aspects making the introduction still difficult for the time being.

Literature and interviews discuss that the trial and error phase to search for the desirable stimulation parameters is difficult, and differs between individual patients, including a different protocol and time span for each patient during the search for optimal stimulation. It seems plausible with more research to give rise to guidelines for average settings to start stimulation. Although there are uncertainties and trial and error will remain practice for now, this will probably not hinder the introduction of DBS. More knowledge about the stimulation settings might have an advantageous influence on the outcome, and maybe on the duration of the procedure.

Another difficult issue in the scenarios is the patient selection. There is no actual definition for treatment-resistant depression and it is unknown, which patients will benefit from DBS. The inclusion

and exclusion criteria constructed in studies by different research groups, and explained by the researchers in the Netherlands during interviews, are similar. For now, it seems plausible for the patient selection process to be similar to current criteria used in experiments. It seems plausible as well that technique such as MRI or biomarker measurement to influence the inclusion criteria will be included in treatment scenarios in the future. However, this is less plausible for the time being, because there is no guarantee that these technologies will be beneficial.

Insurance companies can give guidelines for embedding in the care practices, resulting in a small change of the scenarios, which I consider plausible in the current proposed situation. Although all interviewees argue that DBS will only be possible for the severe treatment-resistant depression, this could potentially change over time. It seems plausible that DBS starts as a treatment for a very specific group, but it can be desirable to change this when more information and knowledge is acquired about the treatment and its effect. However, the interviewees believe that it will never acquire the same status as medication. The plausible scenarios compared with the experimental settings will not include DBS in an earlier stage for now, partly due to the lack of proven effectiveness and partly due to the lack of acceptance by insurance companies. DBS as a mood enhancing technology, as DARPA suggests for military personnel, seems implausible as well. Not only due to the limited knowledge about brain regions involved in depression, but also due to the lack of proven effectiveness for the severe depressed patients. DBS as a non-medical application seems perilous, this is further discussed in the next chapter.

Overall, the clinical practice will change after embedding a new treatment option to treat patients with depression. A new treatment might involve different actors in the psychiatric work field; for example, in the case of DBS, the neurosurgeons who have to perform the surgery and implantation. The practice of psychiatrists will partly change due to an extra treatment option for depression. It seems plausible to add DBS for depression to the current health care system, but more research is necessary to define the patients who can be included for the treatment as well as to define stimulation settings.

6. Desirability

Desirability is the third and last part of the assessment developed by Lucivero et al. (2011). The Merriam-Webster dictionary defines desirability as (1) "having good or pleasing qualities or properties", and (2) "worth seeking or doing as advantageous, beneficial, or wise." This assessment focuses on how the impact of a new technology is normatively evaluated by the actors (Lucivero, Swierstra et al. 2011, p. 136). Dobbs (2006) claims, that DBS shows an incredible rate of effectiveness in very severely depressed patients. With this statement, he underlines the desirability of the technology. Lozano and Mayberg as well claim, during an interview in 2015, that the technology seems desirable, because "It should offer a lifeline to people who might otherwise be doomed to endless despair."

Lucivero et al. (2011, p. 137) argue that the understanding of the benefits of a new technology do not need to be unanimous, different issues might influence users' evaluation of the technology. Physicians and patients, for example, may have a different view on what constitutes a desirable treatment; different values might influence their acceptance of DBS for depression. DBS raises questions concerning issues such as the impact on daily life, practical routines, experience of their bodies, power relations, and responsibilities. These issues might have an influence on the desirability. Pressing ethical issues can cause a non-acceptance. It is possible that different actors accept DBS as a treatment for depression, but this acceptance does not guarantee ethical acceptability because of the values of an individual actor. I investigate the acceptance of DBS treatment by issues discussed by the different actors during the interviews.

The issues I discuss in this chapter are quality of life, personal identity, informed consent, and enhancement. I have chosen these issues based on the discussions during the interviews. Literature considers other ethical implications as well, but I will only focus on the discussions of the interviews to overcome speculations. Mainly due to time constraints, I have taken the expressed values of different actors for granted and do not investigate the techno-moral change. The given arguments are used to investigate the pressing issues that might influence the general desirability of DBS as a treatment for depression, and answer the question, 'Is it plausible for DBS to be a desirable treatment for patients with depression?'

6.1 Implications that Influence the Acceptance of DBS by Different Actors

This section will show an analysis of the issues quality of life, personal identity, informed consent and enhancement. I compare the issues as discussed during the interviews with the ethical literature on DBS. I used literature specific on DBS for depression as well as more general on DBS. Similar to the previous chapter, I quote interviewees and mostly use the shared arguments.

6.1.1 Improvements in Quality of Life

The first concept I discuss is the quality of life. Although not directly questioned, different aspects discussed during the interviews could influence the quality of life. The aspects I consider influential on a patient's quality of life are the battery life of the device, possible changes in social life, and side effects. I focus on these issues based on the discussions I had during the interviews. The battery has the potential to influence the life of the patient. When a non-rechargeable battery is implanted, the patient needs surgery every time the battery dies. Although this is inconvenient, the alternative, rechargeable battery needs charging every day. Researcher 1 states, "It is possible that a battery needs to be recharged 1-1,5 hours a day, and that is very inconvenient for the patient." A patient has to incorporate this habit in his daily life and routines, and has to sit next to a charger every day for example after dinner or in the morning. Each patient can develop his own routine, but all patients have to remember to recharge to prevent a relapse of the depression. Some patients would not consider this a major issue, but the patient should consider this disadvantage before implantation. This makes the patient able to reflect and adjust his daily routines after implantation more easily.

Another aspect is the potential change in the relationship with relatives–especially romantic partners. Patients suffering from severe depression are, in many cases, dependent on their relatives due to their diminished social life. Less depressive feelings might influence contact with relatives and friends positively, but it can have negative consequences as well. There are cases in which patients and their partners have separated due to the sudden change in the patient. In a case outlined by different researchers during the interviews, one particular patient became more active after treatment. This new situation was difficult for the partner and led to a separation. Although Researcher 3 sees this as a negative side effect and undesirable, it can be questioned whether living with a depressed person is the life someone desires or not. As Researcher 1 claims, "We will not keep someone a bit depressed to make a partner happy; we treat the patient." Overall, the changing social life of a patient might possibly influence the quality of life. More research into this topic is necessary to investigate the social life after DBS for patients with depression, but it is plausible that this might influence the desirability.

For patients with treatment-resistant depression, there are no currently accepted treatments. DBS can cause harm due to surgical risks, and there are potential side effects of the stimulation. However, as Physician 2 argues, current treatments such as antidepressant drugs or ECT have side effects as well. A major side effect of ECT is loss of memory. Physician 2 does not consider memory loss beneficial, but if the patient has recovered in part from his depression, he could decide for himself whether to continue treatment or not. The situation is similar for DBS; the patient has to consider whether side effects of DBS are worth the benefits of the therapy. Patients might make decisions partly based on quality of life grounds, and affect the overall desirability of DBS for depression.

I will compare this idea of most interviewees about how the overall quality of life will improve, even with the possible consequences for daily life, to the scientific and ethical literature. Literature does not discuss the battery issue, but there are discussions about the effects that DBS has on the life of the patient (social life and side effects). Lozano et al. (2008, p. 461) claim that patients with treatment-resistant depression have a decreased quality of life and an increased rate of mortality caused by comorbid disorders and suicide. There are different aspects that might influence a person's wellbeing– for example, the treatment's influence on the social life of a patient–and these aspects should be taken into account with the discussion of quality of life. Glannon (2009, p. 290) gives an example of a Dutch patient treated with DBS to overcome tremors who was forced to choose between loss of motor control and mania (a side effect). The choice was between two evils, and in the end, the patient decided that being on the stimulator was better than being off (o.c.).

Wells et al. (1989) have studied the quality of life in a group of patients with depression, and a second group of chronically ill patients. The outcome of this study shows that the depressed patients rate their quality of life worse than other patients do. Depression has a significant impact on the quality of life; depressed patients often feel physically impaired or have less desire to maintain social relationships (Naumann and Byrne 2004, p. 162). Kennedy et al. (2011) show in their research that physical function improves in an earlier stadium compared to social functioning and emotions (o.c., p. 507). Although there is an improvement in the overall functioning, it is unknown whether most patients consider physical or emotional functioning more important. I can imagine that the feeling of emotions is important for patients with depression. However, no study questions this aspect, and more research is necessary to analyze the desirable effect based on quality of life grounds.

6.1.2 Personality Changes after Electrical Stimulation

The interviewees compare personal identity change in DBS with other treatments. Developer 1 argues that different antidepressant drugs may have undesired side effects and result in a change of behavior or mood. Similar risks are involved with electrical stimulation in the brain, but it is easier to manage the effect. Similar to stopping or changing medication, the physicians can stop or adjust the stimulation when admissible effects occur. "It seems to have a more direct influence on the brain, but mood and behavior will probably change in all cases," states Developer 1. He argues that treatment of depression will always induce a certain change, but the question is whether or not this is a change of personality.

Only Physician 3 believes that we need to evaluate personality changes during stimulation treatment. He argues that the discussions concerning changing emotions influence the acceptance of DBS, especially for society and patients. It is clear that you want to change some aspects in the emotional state of a depressed person, but Physician 3 asks, "It remains an ethical question to what

extent do we change someone's personality in a different personality?" The psychiatrist needs to evaluate all occurring effects of DBS on the patient including physical, social, and emotional functioning, and analyze the 'normal' for each individual. The psychiatrist should also evaluate the desirable and undesirable effects of the stimulation on the patient, and his behavior. Consulting close relatives of the patient might help to evaluate the 'normal' of each individual patient.

Physician 1 counters personality changes by claiming that "Someone's personality will remain the same. The tolerance towards impulses might change, but someone's actual personal characteristics remain." Researcher 2 argues that the aspect of personality in cases of patients with Parkinson's Disease is different considering patients with depression, probably due to implantation being in a different brain region. Researcher 2 argues that stimulation will include a change of personality to the premorbid state, but that it is difficult to determine the desirability of the change.

Researcher 3 argues that depressive patients are unhappy due to a suppression of their normal emotions, and that DBS can help to stop the suppression and restore the emotional state of that patient. However, he explains that it is possible for patients to get out of control. He argues that "We need to find the balance between depression, normal, and out of control." The patient has to experience the feeling of 'normal' with stimulation (Researcher 3). If that is possible, it might influence the desirability. As I already suggested, the psychiatrist and the patient need to search for the 'normal' during an evaluation of the depression. Together they can determine whether an effect is desirable. Concluding from the interviews, personality changes may remain a pressing issue in the care of all patients receiving DBS treatment, but particularly in cases of severe depression. Even though change of mood is often desirable, a change towards mania is not.

The possibility of personality change is one of the most discussed ethical issues with DBS in literature, probably because the problem of personal identity is created by taking changes as a negative side effect (Synofzik and Schlaepfer 2008). DBS can result in a mood change, but in some cases, this side effect is the desirable effect. Several ethicists discuss personality changes that potentially accompany DBS. Schermer (2011, p. 2.) states that "Some of the changes that DBS can bring about in personality, cognition, behavior, or mood may actually be sought by the patient and be the goal of treatment, for example mood improvement in depression." Though changes in cognition, behavior, or mood are occasionally objectionable, some are unproblematic and even desirable with neurological disorders such as depression. As argued by the interviewed physicians, literature as well state that DBS can restore the personality of a patient with depression to its premorbid state (Johansson, Garwicz et al. 2011). The important question with DBS is not whether someone's personality changes, but whether a patient perceives himself as different when compared to the pre-depressive period.

Kraemer (2013) discusses personality with DBS in general, and claims that patients are trying to feel like themselves for the first time in their lives. If someone feels like 'himself' for the first time, this implies that the patient perceives himself different. Kraemer (2013) goes on to discuss the experience of the patient after stimulation not as desirable or non-desirable, but she argues that patients like to have the chance to 'be who they really are'. Quoting one patient, "In my previous life, before stimulation, I did not dare to do such things. I live a well-adapted life; a life which I now see was never really mine" (o.c., pp. 758-759). Kraemer (2013) suggests that patients may perceive themselves differently, but feel more like themselves. This makes the process to search for the preferred stimulation settings and the 'normal' of a patient even more difficult. It should be determined beforehand how the physician and the patient come to a final verdict about the desirable stimulation settings. It is important that the patient plays a role and indicate his preferences. However, the psychiatrist should have a verdict as well and share this with the patient.

Another question is not whether or not there is a chance of personality change, but whether or not the patients see this as a problem. Lipsman et al. (2009) have investigated the alteration or loss of personality by patients before and after neurosurgery in general. They found that personality change was not usually a concern for the patients; the main concern of the patient was about the surgical risks (o.c.). A patient once argued, "I can't worry about that at this point ... the positive aspects of having this operated on far outweigh any concerns I have about personality change" (o.c., p. 379). I think that someone might have a change in mood or behavior compared with the depression, but possibly not compared with the situation before the depression. Still, it is acknowledged that DBS might result in a personality change. Therefore, it is plausible that the discussions of DBS for depression present personality change as a pressing issue for the psychiatrists as well as the patients. This discussion should include the possible conflict between patients and psychiatrists to set the desirable stimulation. A search for the 'normal' for each patient is necessary, but the standards of a patient can potentially shift, resulting in a different preference of the simulation settings.

6.1.3 Mental Competence Makes Informed Consent Difficult

Patients must give a voluntary informed consent for the entire DBS procedure in order to receive treatment. This includes all aspects of the surgery and the steps before, and all stimulation steps as well after surgery. In addition to the procedure, the patient should be aware of the risks and possible side effects regarding surgery or stimulation. All interviewees see the aspect of an informed consent as required. A DBS treatment under duress is not possible claim Researchers 1 and 2, a patient needs to give his informed consent. The remaining question in the case of treatment-resistant depression is whether someone is competent to make such a decision and give his informed consent. Researcher 1 does not consider this problematic, and says that "Although depression can result in a negative view, someone with a depression is in principle mentally competent to make decisions." In contrast,

Researcher 2 believes that informed consent is sometimes difficult, and says, “We have to be attentive to the decision-making capacity of a patient, possibly influenced by the depression.” He explains that in some cases the situation seems desperate for the patient, influencing the capacity to make a well-thought-out decision.

Health care provider 2 sees this vision of last resort as a possible problem as well, and claims that “When someone is already suicidal, he would probably have no problem with DBS.” He argues that the treatment-resistant, and probably suicidal, patients would take every opportunity. Therefore, it remains important to give the patient all available information about DBS and the possible inconveniences. This allows the patient to make a deliberate decision and not grab every opportunity without thinking it through. The interviewees all agree that the majority of patients with treatment-resistant depression are capable of giving informed consent with or without the consultation of a relative, and they consider the physicians capable of providing all available information that can help the patient make a decision. However, the idea that DBS might be the last resort for the patients is plausibly influential for the desirability.

For the most part, literature agrees with this view of the interviewees. Nuttin et al. (2014, p. 3) also claim that an accurate informed consent of DBS in psychiatry is necessary. “The patient should understand that neurosurgery for psychiatric disorders aims for a symptomatic treatment of psychiatric impairment, but may not be able to ‘cure’ the disease process.” The physician has to be careful with his description of the outcome, and makes the patient aware that there is the possibility that he might not benefit at all. Although a physician is capable of providing all relative information, various factors might influence the decision of the patient. Schermer (2011) discusses instances when an informed consent for DBS as treatment for depression can be problematic. First, she argues that it can be a desperate decision because of the hopeless situation of the patient. The decision to undergo DBS treatment is probably at the end of the treatment protocol, and patients often feel that there is no other option left (o.c.). This statement concurs with the arguments some of the interviewees about last resort treatment option. Second, media report might cause a raise of hopes and expectations of DBS to unrealistic levels (o.c.). I do not consider this as a large problem when the physicians make the patient aware of the risks, benefits, side effects, and limitations. Third, different neurological disorders or comorbid disorders can challenge the patient’s competence to give an informed consent (o.c.).

Appelbaum (2007) studied the decision-making capacity of patients with depression. He argues that it might not be as problematic as some believe. There are legal standards for decision-making capacity for consent to treatment, including the ability to communicate about a choice, the ability to understand the relevant information, the ability to appreciate the medical consequences and the situation, and the ability to reason about treatment choices (o.c.). Before informed consent, the responsible physician should evaluate a patient’s competence in order to protect him from negative

consequences. Appelbaum (2007, p. 1835) claims that "Only patients with impairment that places them at the very bottom of the performance curve should be considered to be incompetent." It is possible that severe depression results in incompetence, but a physician has to determine this for each individual patient, and may consider contacting relatives in order to do so.

Overall, the literature and the interviewees value the capability of physicians to provide all of the information for a deliberated, informed consent. This deliberated process has the potential be problematic for some severely depressed patients; therefore, a physician should determine the decision-making capacity before the informed consent. The impression of the psychiatrist considering the mental competence of the patient might result in consequences for the patient selection. For example, in a case where the patient is not competent to give informed consent, resulting in a difficult position for the physician. In such a case, the psychiatrist has to decide whether to withhold the DBS treatment from certain patients, even though they might benefit from the therapy. It is not very plausible that the discussion of informed consent and competence for consent will influence the desirability of DBS for the patients because this is already practice in the current health care system, but it can have consequences for psychiatrists and their view of desirability for the embedding of such a treatment. Physicians should consider this aspect before the embedding of the technology and reason how to cope with difficult situations.

6.1.4 Improve the Mood or Capabilities of Healthy Individuals

Mood enhancement was not discussed spontaneously during the interviews, but when I asked for the opinion of the interviewees on enhancement possibilities, the reactions are similar. The interviewees see DBS as a treatment only for patients suffering from an ailment, and in the case of depression, only for the treatment-resistant. However, Developer 1 considers mood enhancement an interesting ethical question, because patient selection is not standardized and requires specifications before embedding into the health care system. "All speculations of enhancement, including improvement of function and the erasing of memories, is tricky business and a difficult issue" states Developer 1. He leaves the subject open, but sees the question 'Why we will not treat other patients?' as something difficult to answer. Researcher 3 argues that "DBS will have a future, but it is too premature to implant every child with electrodes to overcome disorders or improve capabilities." He is very clear that he only considers DBS possibly beneficial for patients with treatment-resistant depression. We should not use such a technology as a normal treatment for all patients and surely not for healthy subjects.

In contrast, ethical literature regarding DBS frequently discusses the issue of mood enhancement. Synofzik and Schlaepfer (2008, p. 1516-1517) argue that DBS in psychiatry has the potential to open doors into more applications in the future. Possible examples of these applications would be to

ameliorate psychiatric disorders, as well as enhance mood and cognition in healthy individuals. Kraemer (2013, p. 760) also claims that it is possible that "One day DBS may even be used for enhancement purposes." Synofzik and Schlaepfer (2008, p. 1517-1518) contradict this claim with the use of the bioethical criteria of beneficence, non-maleficence, and autonomy. With respect to these issues, they conclude that DBS is not yet ready to use for mood enhancement purposes. One of their counterarguments is that the risk of harm weighs much more in the potential case of enhancement (o.c., p. 1517-1518). A patient with treatment-resistant depression is more likely to benefit from DBS than a mentally intact person. There is currently not any evidence that shows effectiveness for enhancing mood or cognition of healthy individuals (o.c.). Although they see no evidence, Liao (2014) presents the expectation that DARPA will use DBS to treat psychiatric disorders in soldiers, and once that is possible, to use DBS to fortify soldiers' minds by the detection of emotional reactions. I already discussed in the previous chapters that this expectations seems technologically as well as socially not plausible. Overall, there is a concern of enhancement raised in literature, but I think we should not take this as a pressing issue for the time being. Enhancement is not justified in the current health care system as well as not plausible to become desirable due to the harm it can cause in healthy individuals. Ethics should focus on the plausible use of DBS technology, thus use in clinical settings. It seems not plausible to accept the use of DBS technology to enhance healthy individuals.

6.2 Issues that might Hamper Desirability

The goal of this chapter was to assess the plausibility that DBS for depression is generally considered as a desirable therapy. On one hand, the papers concerning experiments present this treatment as a promising and wanted therapy. On the other hand, there are several ethical issues discussed in literature that concern DBS in general, and some are more specific to DBS for depression. I have compared the issues discussed during the interviews to this literature. Based on these two sources of information, aspects of quality of life, personality, informed consent, and enhancement seem influential on the general acceptance of DBS. Each patient's quality of life requires continuous evaluation during treatment to analyze whether or not the quality of life changes. Quality of life is primarily important for the patients, but psychiatrists are responsible for considering this issue and evaluating the depressive state of the patient. It will remain an important issue, and the understanding of specific values of patients is possible with additional interviews. A weakness of this thesis is the lack of interviews with patients. In addition, in order to investigate the quality of life in detail, further knowledge about the long-term effects and side effects of DBS for depression is necessary.

Several ethicists discuss the issue of personality change as something problematic in general, but inherent in cases of patients that are recovering from depression. In contrast, the interviewees do not consider personality change as problematic in the treatment of depression. The interviewees are unequivocal in stating that the personality does not change, but that the patient has the potential to

become, or at least feel like, his actual self again. The remaining difficulty is determining 'normal' for each patient. It is likely that identification of the normal remains a pressing issue in the discussions considering the desirability of DBS for depression, for example, in cases where a patient and a physician have a different idea of a desirable outcome. As shown in literature, patients have the potential to feel like themselves for the first time in their lives, and experience this as desirable, but that is probably not the 'normal'. All effects caused by the stimulation require attention and need to be examined in order to determine which stimulation settings are optimal for each patient.

Informed consent is an important topic, and discussed before almost every treatment within the health care system. All interviewees agree that informed consent must be included. However, this probably does not result in any difficulty, because it is already practice in current care and experimental settings. With respect to DBS, the difficulty lies in answering the question of whether or not a depressed patient is mentally competent to make the decision to participate in DBS treatment. Interviewees and literature agree that depressed patients are capable of making a deliberate decision for this radical treatment. However, it is possible for competence to be affected by depression. Therefore, the mental competence of patients should be evaluated in all cases. This procedure might influence the psychiatrist, who may choose to withhold the therapy from certain patients.

Enhancement is currently not justified in the health care system. It seems unacceptable to use DBS as an enhancement technology to improve mood and/or cognition in healthy patients. There are discussions concerning the option of mood enhancement, but we should not focus on this issue for now. As before discussed, I suggest that the DARPA expectations to use DBS as a preventive technology implausible. More knowledge about the brain processes involved with the disorders and the influence of DBS on different brain regions is required before the issue of mood enhancement could become plausible. I consider the idea to enhance the mood too speculative, thus, to overcome speculative ethics, we should not focus on enhancement in current (ethical) discussions considering DBS for depression.

Health care currently has procedure for and applies informed consent, especially for the more radical treatments. DBS might become a radical therapy for patients with depression and probably only accepted for treatment-resistant depression. Informed consent, and the evaluation of a patient's mental competence to give such consent, both require some attention, but they do not comprise the most pressing issue. Although a change of emotional state seems desirable, issues of personality change and quality of life remain important. The psychiatrist needs to investigate all effects of stimulation on each patient's behavior. I consider it plausible that the issues of mental competence, quality of life, and personality change influence the desirability of DBS treatment; however, a more substantiated answer to the question of desirability requires further research, including an analysis of the values based on a higher number of interviews with depressed patients.

7. Conclusion

The goal of this thesis was to analyze the desirability of DBS as a treatment for depression. I have done this by investigating the plausibility of the expectations of DBS treatment with the use of a plausibility assessment developed by Lucivero et al. (2011). This approach was to overcome the problem of ethical research going along too easily with speculations about new technological developments. This thesis has focused on an analysis of the expectations in scientific literature and media. I have performed a literature study and several interviews to answer my research question, *"How to assess the desirability of current expectations about Deep Brain Stimulation as an emerging treatment for depression while avoiding speculative ethics?"* With this question, I wanted to distinguish between plausible and implausible expectations, and gain knowledge of how to assess the desirability of DBS for patients with depression. The analysis of the plausibility of expectations provided guidelines to define the most pressing ethical implications and helped to develop an agenda to guide the discussion about this technology.

To investigate how to evaluate the desirability, the first step was to assess the plausibility of the expectations about DBS for depression. The assessment consisted of three different parts, namely, assessing the technological feasibility, social usability, and desirability. First I investigated the plausibility of the expectations that this technology will evolve as a treatment for treatment-resistant depression, and whether the devices might improve. Concerning the technological feasibility, I suggest it plausible that the expectation that several aspects of the technology will improve in a short or long time span, as described in literature. Concluding from the interviews, I consider it plausible that the recharging ability of the battery will improve and that the size of the stimulator will eventually reduce. Aside from the improvements of the stimulator, I assume that the electrodes will change, and thereby the electrical stimulation possibilities as well. It seems plausible that electrodes with 32 or 64 contacts will be developed and used. I assume that this might improve the specificity with which the physician adjusts the stimulation.

Although I can conclude from literature and interviews that technological improvements of the hardware seem plausible and beneficial for the patients, there is a problem concerning the knowledge about the connection between the brain and depression. Taken from literature, I have discussed several hypotheses for a selection of the different brain areas suitable for treatment. Currently, there is no consensus on a specific brain region, methods to select the 'right' patients are lacking, and scientists specify each research in different brain areas. The effectiveness varies greatly and the use of different brain regions makes comparing the result of all research difficult. I assume that the heterogeneity of depression makes the choice for a brain region problematic, but the lack of knowledge and consensus makes the procedure for treatment difficult as well. As the researchers argued during the interviews, it is unclear at the moment which brain region will provide the highest effectiveness and whether or not

this might differ from patient to patient. I consider the expectation that one region will be found suitable for all patients as implausible. Overall, the technology seems plausible for use, but I consider the application in depressive patients as a current trial and error process. As already discussed, it seems evident that more knowledge about the brain and the stimulation is required before it becomes plausible to use this technology in a regular basis for the treatment of depression.

The second part of the assessment focused on the dimension of social usability, in which I investigated the current practice in care of patients with depression, and developed different possible embedding scenarios for DBS as treatment for depression. Based on the current experimental settings, I suggest it plausible to embed DBS for depression in the care of treatment-resistant depression at the very end of the treatment-protocol. All interviewees see this as the best option. In this embedding scenario, it seems plausible that the potential treatment protocol would be similar to the experimental settings, including the issues of brain region and patient selection on which there is no consensus. The overall treatment of patients with depression will remain similar; there is only a change at the end of the protocol. In according to the interviewees, I consider it desirable for patients that DBS might give them an extra chance to recover. Although it is something new and the work field might change, considering the interviews, I assume psychiatrists will accept this high-tech procedure when shown effective.

Next to the plausible script based on experimental settings, there are some more radical scenarios including expectations of the future. There are no results published at the moment, but some research includes imaging technologies, such as MRI, before the implantation. Researchers might use this to compare outcomes of treatment in a certain brain area. The researchers I have interviewed consider imaging helpful to increase the knowledge about the brain areas involved, and the influence of stimulation. Due to a lack of information, I conclude that it seems currently implausible to embed DBS for depression in a patient personalized way, including the use of MRI to determine the brain region for implantation. I consider it plausible for a hospital to specialize in one procedure, and possibly implant the electrodes in one brain region for all treatment-resistant depressive patients.

We can anticipate some difficulties in the plausible script. There is a phase of trial and error before defining the optimal stimulation settings. First, this trial and error phase is time consuming, but concerning the different actors I interviewed, I consider it implausible that this phase will hold up the introduction of DBS. However, this phase can affect patient's experience and the practical procedure. Second, before embedding, health care insurance companies need to accept the treatment and incorporate this in insurance coverage. According to the health care providers, this is a plausible step when the technology is effective. It also seems plausible for the insurance companies to include certain criteria for coverage, such as hospital of choice and patients included for treatment. Third, the patient selection remains a difficult question for the embedding as well. Based on literature and the

interviews, I suggest that it seems most plausible that DBS will only become an option for treatment-resistant depression. Physicians who are responsible for the care of a patient with treatment-resistant depression use a set of inclusive and exclusive criteria similar to current experimental set-ups. For the time to come there are many uncertainties that influence the possible embedding of DBS for depression. The selection is difficult and only a small number of patients is included in the different trials. The effectiveness of these studies varies to large extent, making it difficult to determine whether or not it could become included in the insurance.

The last part of the assessment was to discuss the plausibility that all participants involved consider DBS plausible. As I have shown in the previous chapter, it is not likely that all of the ethical implications discussed based on the speculations about the technology are pressing issues. Some issues seemed important, but different actors I interviewed did not consider these as problematic. One of the mostly discussed implications is personality change. There is a consensus that personality change is something problematic, but inherent in the case of treatment-resistant depression. Physicians I have interviewed claim that DBS treatment for depression will induce a change in the patient, but not in the personality, the patient will only regain his actual self. Although interviewees and some ethicists in literature argue that DBS for depression does not cause personality change, but restore the 'normal', defining this 'normal' remains difficult. Not discussed by physicians, but I assume that this can become a difficult issue for the psychiatrists who have to determine which stimulation settings are the best for a patient. It is possible that a patient feels 'better' than before, and that he believes that the settings work for him. It is discussed during the interviews that psychiatrist might agree with the patient, but it is also possible that psychiatrists change the settings to find out which settings restore the 'normal'. I suggest that physician consults relatives, possibly before the stimulation as well as during the search for the optimal stimulation settings. However, it is still possible that a patient prefers a different outcome. I can conclude from all of the discussions in literature and during the interviews that personality is a difficult issue that might influence the desirability of the treatment for patients as well as for physicians and possibly other actors. In my opinion, the issue personality change needs some consideration during the design of the treatment process, and especially before the embedding in psychiatric care. Psychiatrists have to create a certain 'protocol' how to deal with the observed changes induced by electrical stimulation.

Other issues discussed in the literature and during the interviews were quality of life and informed consent. Quality of life is not discussed directly during the interviews, but seems primarily an issue for patients. However, the psychiatrist is involved as well and should analyze the quality of life with the evaluation of the depressive state of the patient. I consider it as a remaining important issue. In cases of severe surgical side effects, the quality of life can decrease and thereby make DBS less desirable. However, I consider it plausible that DBS creates an increase in quality of life due to

the suggested positive influences on the life of a patient with treatment-resistant depression. However, we should still be careful with this assumption considering the lack of evidence on the effectiveness of DBS for depression.

The issue of informed consent might be difficult in the case of psychiatric disorders because of a possible decrease in the mental competence to make decisions. The possibility that a patient with depression is mentally incompetent is low. I consider the issue of informed consent as implausible to lower the desirability for the patients, but certain aspects are important for the psychiatrists. The psychiatrists have to consider these aspects before informing patients (and relatives) about DBS, as currently done for almost all medical treatments. He needs to determine which information and advice he should give the patient, whether or not the patient is competent to make a decision for the treatment, and possibly the psychiatrist might have to consider withholding a treatment form a certain patient.

Although ethicists argue on several concerns in literature, the interviewees did not seriously consider mood enhancement as an implication of DBS. The technology is justified only for patients and not for improvements of 'healthy' persons. I presume mood enhancement not as a pressing issue in the current situation and does not require inclusion in discussion considering the desirability of DBS. Although DARPA expects that the investigation of DBS for psychiatric disorders might evolve in treatments to prevent disorders, I consider this implausible. There is already a doubt with the technological feasibility, implying that we should not consider this aspect as plausible according to the assessment method. Only the use of DBS in clinical settings seems a plausible expectation.

I have investigated the plausibility of the expectations of DBS as treatment for patients with treatment-resistant depression. The current expectations show DBS as a desirable technology for treatment-resistant depression. However, considering the three domains of technological feasibility, social usability, and desirability, there are some issues with these expectations. As previously discussed, there are several expectations of future developments, such as a closed-loop system or advancements induced by imaging, which are seemingly implausible beforehand and too futuristic. Therefore, I suggest that the most pressing issues we need to include in an ethical agenda for further discussion are brain region selection, patient selection, personality change, and quality of life. First, considering the issue to select the optimal brain region for treatment, I conclude that it is not technologically feasible at the moment to define the most effective region for stimulation. Secondly, another difficult aspect in the domain of social usability is the patient selection. DBS might become an extra option (of last resort) only for the treatment-resistant depressive patients, but there is a lack of knowledge about the suitable selection criteria. Thirdly, a pressing ethical implication, especially with DBS for Parkinson's Disease, but possibly for depression as well, is personality changes. I suggest that all affect the personality and the quality of life might influence the desirability of the treatment.

I suggest that these issues might influence the desirability and therefore need our attention in discussions concerning DBS for depression. The outcome of the discussions can possibly influence the design and/or embedding of the treatment. Further research on DBS treatment for depression is required as well. This thesis has shown brain region selection and patient selection as pressing problematic issues that require research as well as discussions considering embedding. These issues can provide information about the desires of different actors to the designers. I see an increase of our knowledge about the brain, and the patients, as a necessary step before the embedding of this technology becomes plausible. This research provided help to define some guidelines in the protocol to use the technology after embedding.

Several ethical implications require our immediate attention before the embedding as well, resulting in an ethical agenda. I suggest that different actors have to consider and develop an understanding how to deal with the effects DBS has on the patient's behavior and mood (possible personality change) or quality of life for example. The idea to dismiss issues like mood enhancement during the discussion is necessary to avoid speculative ethics. We should focus first on the possibilities and the pressing issues before expecting a fantastic future for DBS for patients with depression. Finally, to assess the desirability I suggest focusing on different issues during the design and the embedding phase of the technology. The brain region and patient selection are influential for both phases and need our immediate attention before we will focus on the ethical agenda.

7.1 Reflection on the Thesis

In the previous chapters, I have analyzed the plausibility of the expectations about DBS for depression. Here I will give a reflection on this thesis and discuss the used assessment as well as the interviews. Followed by some ideas on how to overcome or deal with the possible obstacles for the embedding of DBS in psychiatry and possibly influential for the desirability.

7.1.1 Value of the Used Assessment Method

The method I have used in this thesis is an assessment of expectations developed by Lucivero et al. (2011). The goal of this thesis was to analyze how to assess the desirability of DBS as a possible treatment for patients with treatment-resistant depression while avoiding speculative ethics. The assessment gave the ability to investigate the plausibility of expectations, and analyze the technological feasibility, social usability, and desirability. The goal, as described by Lucivero et al. (2011, p. 130), is to create tools to improve the epistemic conditions for the reflection on desirability of new and emerging technologies. They strive to reach this goal by developing criteria and procedures to avoid the speculative aspects, and by encouraging the imagination of actors involved in the new technologies (o.c.). The question is whether this was a suitable assessment to use in my

research or not. The three steps of this assessment gave me some guidance in the analysis of DBS treatment for depression. However, I could not perform all steps in depth in the time span of this thesis. It was difficult, for example, to encourage the imagination of the actors involved in the interviews. The actors were interviewed in the beginning of the assessment and at this point, I had not yet created the speculative scenarios for the future. I could not encourage and only used the existing, and less imaginative, scenarios for questions. For now, I took the expressed ideas and values for granted, however, further research could focus on the imagination and analyze whether or not I should change the conclusion in view of potential techno-moral change.

A difficulty with the assessment is the overlap of issues within different dimensions. Take, for example, the difficulty of brain region selection. This aspect can be seen as technologically implausible, but it has implications for the embedding of the technology in the psychiatric care as well. From a technological aspect, it can have consequences for the effectiveness, but it can have implications for the patient selection after embedding of the treatment. It is difficult in this assessment to know in which dimension we need to include a certain issue. Thereby, all different issues discussed in the technological feasibility and social usability chapters can have an influence on the desirability as well. In spite of the small difficulties, the assessment was suitable for this thesis.

The assessment to assess the plausibility seems suitable to answer the question of this thesis. It is helpful to assess the technological and societal issues in order to exclude the more speculative aspects of the new technology–for example, by taking only the feasible technological developments or scenarios for care into account. I can conclude that the expectation for the technology to be sensible and detect signals of depression is implausible. However, this improvement will cause fewer side effects what can make DBS less harmful and more desirable. I suggest that, due to the implausibility of this technological development, we should not take this issue in further discussions; the assessment method suggests this as well. We should focus on the feasible technology, and if and when sensible detection becomes possible, take this aspect into account then.

I think that the assessment could give guidance in more stages of the development. I suggest using this assessment in a later stadium of the development and possible embedding as well. More research is currently being conducted, some of which includes MRI as a useful tool. The results of these measurements are not published yet. If it does prove to contribute additional value, the imaging step can be important and result in improvements of the technology and/or treatment. It is possible to use the assessment used in this thesis again, and evaluate the plausibility of rising expectations. This step will give guidelines to assess the actual desirability by different actors. However, this last part remains a difficult step, to disentangle desirability and plausibility. The assessment not directly assess the desirability, it assesses the plausibility of aspects or expectations that might influence the desirability. This plays a role in the whole assessment, but especially in the last domain.

7.1.2 Involving more Actors in the Interviews

The primary remark regarding the interviews is that I could have done more interviews, and it would have been especially beneficial to have interviews with patients. I have reached a couple of researchers and physicians involved with the experiments of DBS for depression, but the number of physicians not involved with the research was already small. Although I interviewed psychiatrists who were not involved with the experiments, they had a high interest in the technology. It is possible that this will be different when I would have had the opportunity to include more actors. Regarding the patients, it was very hard to contact patients with depression. I have tried to reach them via forums for depression or via patient organizations, but I did not have any luck. I still think that via these organizations is the best option to contact patients. A different approach would be helpful as well, however, via psychiatrists in the hospitals it is only possible to contact the severe depressed patients. A possibility is maybe via an institution where less severe patients are treated, to place an announcement with a call for interviews for example. Another option is to make a survey. Although the survey would be accessible to more people and the threshold to fill in this survey is lower, the information acquired is smaller and it is not possible to ask for explanations.

In spite of the small number of interviews conducted for this thesis, the questions asked were usable for the analysis (see appendix B). I updated the questions after each interview and adjusted them to the actors in question. It may have been helpful to perform a part of the interviews before the analysis and another part during the analysis in an effort to stimulate the imagination of the interviewees. It was fine for this thesis, but in the future, I suggest performing some interviews in a later stadium to investigate certain aspects in more detail, and provoke the imagination of actors.

7.1.3 Dealing with Possible Undesirable Obstacles for Embedding

The aspect of brain region selection extensively discussed in this thesis, but a remaining question is how to translate this problem to clinical settings. I assume that there are different options to handle with this aspect if we want to embed DBS before more knowledge is acquired. The first option is similar to the current experimental settings. Each hospital exclusively implants the electrodes in one brain area. This would increase the physicians' knowledge of that specific area, and the outcome of stimulation of that specific area. However, this might introduce difficulties for the patient selection and the advice a physician gives his patient(s). It is possible that one hospital might not include a patient due to the selection criteria, but another hospital with an implantation procedure in a different brain region might include this patient. In light of this theory, should the physician inform the patient about other procedures in other hospitals, possibly with an implantation in a different brain region? This would make it more difficult for the patient, especially because it is currently unknown whether a treatment in a different brain area is more beneficial than treatment in another. To overcome the

problem of advice, a hospital might choose the other option. The physicians will not specialize in one brain region, but be knowledgeable about several possible spots for implantation. Although it seems beneficial to have a patient-specific treatment, this is currently not plausible due to the lack of knowledge about depression and the brain regions involved. This makes it more difficult in the information a physician can give to his patient about the reasoning for choosing one area over another.

This is not the only aspect that can make the work of the psychiatrist complicated. In current care of patients with depression, the psychiatrists only enter the operation room for an ECT. If and when DBS might be embedded in the psychiatric care, psychiatrists would have to enter the operation room for a more radical procedure. Their weekly routine would require adjustments to accommodate this long surgery. However, the surgery is probably not a standard occurring event in their weekly schedule, so this needs some attention. Besides the more logistic difficulty and adaptation of the psychiatrist to a surgical procedure, the psychiatrists have to learn to work with the new technology. This includes treatment options, all risks and possible benefits, and the whole procedure before and after surgery, including selection of the patients and the determination of stimulation settings. The neurosurgeon would implant the devices, with whom the psychiatrist would have to build a professional relation. They need to communicate about the surgical procedure for each patient before the treatment, and the neurosurgeon might be able to assist and advise the psychiatrists during the trial and error phase to determine the stimulation settings.

The psychiatrist and neurosurgeon are probably both involved in the selection of the patients before surgery. However, the criteria for selecting patients can change over time based on results of new research. The hospitals have to respond to this and need to change practice when necessary, for example in the case of the introduction of imaging in the process for selecting patients for treatment. I suggest that this makes it even more difficult for a psychiatrist to explain when DBS is not beneficial for a patient. Shown effectiveness in an earlier stadium and more patients included could introduce new obstacles. Most interviewees consider this implausible at the moment, but some make suggestions that DBS can obtain a similar position to ECT in the treatment protocol. We do not have to consider this issue as pressing, but DBS in an earlier stadium might introduce other difficulties. The selection probably becomes even more vague. Thereby, patients would ask for this treatment during ‘failing’ pharmacotherapy. Especially in such a situation, the physician might have a difficult task to advice the patient and determine the grounds for exclusion. In my opinion, this seems a less desirable situation for the patients as well as the physicians.

This situation can cause some friction, but also compared to the current care of patient with depression, DBS can cause friction. I consider the fact that DBS comes with many new working conditions plausible, but DBS will require a different evaluation of the conditions of the patient. Electrical stimulation will cause several effects, including effects on the behavior and mood of the patient. All of these effects need to be evaluated; not only the personality, but also all other effects the

stimulation has on the patient and his quality of life. This is probably similar to treatments with drugs or ECT, but a difference is easy adjustments of stimulation settings. With this, the effects are changeable, possibly resulting in a conflict between the desires of the patient and the interpretations of the psychiatrist. As discussed before, the psychiatrist will likely search to regain the 'normal' of the patient, but the patient can have a different view and likes the 'better'. These different desires can result in a friction in the relationship between patient and psychiatrists. To overcome undesirable situations, psychiatrists could make a kind of protocol for himself for how to cope with a situation in which the patient has a different opinion than the psychiatrist about the stimulation. The relationship does not change in the way that he involves the patient in the treatment procedure, but the patient might have a larger role in the evaluation and next step of the treatment (in this case, the change of stimulation settings). The role of the relatives might become larger as well, as they can provide the psychiatrist with information about the 'normal' of the patient before the depression. I assume that it might become common practice to develop a profile of the patient's personality before the depression, before DBS treatment starts. However, in all cases, the psychiatrist needs to inform the patient about the process after surgery as well as how he will evaluate the depressive state and conditions of the patient. This makes the informed consent even more important, but can reduce the possibility that the patient and psychiatrists end up in a conflict during the treatment process.

In spite of these ideas to deal with certain obstacles for embedding, the actual use of DBS in the care of patients with treatment-resistant depression is still not possible. As already discussed, the actual embedding seems problematic due to difficulties in technological feasibility, especially the brain region selection but also the patient selection is a pressing difficult issue. To assess the desirability, I suggest focusing first on research for clinical use to improve the knowledge about depression and DBS, and the influences on the brain. Although I consider it plausible to embed DBS for depression in a way that is similar to the experimental settings, the issues of brain region and patient selection probably influence the desirability of the treatment. An agenda including these issues considering DBS for depression could provide the acquiring of more knowledge about the desirability. Possible influential ethical implications, such as personality change and quality of life, might be included in the agenda for assessing the desirability as well, however, first more research and knowledge about the technology, the brain, and treatment possibilities is required and might help to guide the arguments.

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Appendix A – Expectations about DBS

The success of DBS as a treatment for Parkinson's Disease or Obsessive Compulsive Disorder, may give the impression that there are inevitable consequences on the scientific and medical progress (Gardner 2013). Expectations of DBS as a treatment for patients with depression can occur and influence the scientific, public, and ethical domain. There is a possible overlap between the three groups and therefore I chose to include the expectations published in scientific papers (within the scientific domain), expectations published in public papers (within the public domain), and ethical expectations published in academic papers (within the ethical domain). An overview of expectations about DBS for depression and arguments that may result in speculations affecting the three different areas is given in this table.

Scientific area	**Public area**	**Ethical area**
"The effect of surgery on the patient's clinical symptoms and signs of depression was dramatic and occurred after insertion of electrodes" (Jimenez, Velasco et al. 2005)	"Now a revolutionary treatment that entails brain surgery shows preliminary promise in treating intractable depression" (Trudeau 2005)	"Quality of life may actually decrease after surgery, even when physical symptoms improve" (Schermer 2011)
"Although DBS to the nucleus accumbens did not 'cure' their depression, it remains the only treatment option so far that has minimized levels of depression in many years and many different treatment attempts" (Schlaepfer, Cohen et al. 2008)	"An incredible rate of effectiveness in patients so immovably depressed" (Dobbs 2006)	"Changes in behavior, mood, or cognition caused by DBS might result in changes in personal identity" (Schermer 2011)
"DBS is adjustable and stimulation is reversible. These features increase safety and may offer advantages for both the efficiency of the therapy and its acceptance in the patient, medical, and psychiatric community" (Lozano, Mayberg et al. 2008)	"Regardless of how it panned out in the clinic, Mayberg and Lozano's DBS study is already changing how neuroscientists and psychiatrists think about depression" (Dobbs 2006)	"DBS can change a patient's mental state in a groundbreaking way" (Kraemer 2013)
"It is less invasive, fully removable, and adjustable" (Synofzik and Schlaepfer 2008)	"Clinical and behavioral effects were robust, the procedure was safe, and correlative imaging results supported the initial hypotheses" (Mayberg and Lozano 2008)	There is a conflict of interest. "Even though companies may economically support a clinical study to benefit the interests of the patients, it is undeniable that a legitimate commercial interest in making a profit coexists" (Nuttin, Wu et al. 2014)
"The results of this multicenter investigation of DBS of the VC/VS region provide encouraging preliminary evidence of a sustained therapeutic effect in an otherwise highly treatment-resistant population" (Malone, Dougherty et al. 2009)	"Images from popular fiction such as One Flew Over The Cuckoo's Nest or The Manchurian Candidate (…) may influence the public perception of DBS" (Schermer 2011)	"Mood enhancement brought about by DBS does not really improve well-being" (Schermer 2013)

"Successful treatment of a severe treatment-resistant depression with verified functional modulation of the major afferent bundle of the LHb" (Sartorius, Kiening et al. 2010)	"Though the total number of patients is still small, we are encouraged by the results" (Patoine 2012)	"It could possibly be used not only for ameliorating psychiatric disease states, but also for enhancing mood and cognition in healthy subjects" (Synofzik and Schlaepfer 2008)
"The findings of this study support the long-term safety and antidepressant efficacy of subcallosal cingulate DBS for TRD and suggest equivalent safety and efficacy for TRD in patients with BP" (Holtzheimer, Kelley et al. 2012)	"Deep brain stimulation is emerging as a viable option for treatment-resistant depression" (Moss 2013)	"Doctors should limit themselves to treating disease and not wander beyond that into the realm of enhancement" (Schermer 2013)
"SCG appears reasonably safe and shows considerable promise in helping patients with TRD" (Lozano, Giacobbe et al. 2012)	"DBS has shown efficacy when targeting different regions in the brain, and this may be explained by the very heterogeneous nature of depression symptoms" (Moss 2013)	"Feelings of authenticity that can arise under treatment deserve respect as central preference of some DBS patients (…) feelings of authenticity and alienation under treatment is of considerable heuristic value for healthcare professionals and ethicists" (Kraemer 2013)
"DBS to the NAcc has demonstrated sustained antidepressant effects over up to 4 years in a small sample" (Bewernick, Kayser et al. 2012)	"Unintended side effects have also spurred new uses of this poorly understood technology (…) obesity has become an enticing target for DBS" (Fisher 2013)	"Patients have to give their voluntary and fully informed consent (…) this may be problematic for several reasons" (Schermer 2011)
"LMFB-DBS might be a safe, highly efficacious alternative method for treatment-resistant depression, associated with a rapid onset of action" (Schlaepfer, Bewernick et al. 2013)	"The most radical breakthrough is deep brain stimulation (…) absolutely astonishing results with people who failed every other kind of treatment" (Solomon 2014)	"In DBS for psychiatric indications modification of personality is not an unwanted, coincidental side effect (…) the ethically decisive question is not whether DBS alters personality or not, but whether it does so in a good or bad way from patient's very own perspective" (Synofzik and Schlaepfer 2008)
	"Although the technology has become more refined, deep brain stimulation is still associated with surgical risks and psychiatric complications as well as high costs" (Horgan 2014)	"Alteration or loss of identity was generally not a concern for patients about to undergo a neurological operation" (Lipsman, Zener et al. 2009)
	"People who had been suffering profoundly (…) were now describing feelings of rejuvenation, of looking forward to something new and exciting" (Wrobel 2015)	
	"It should offer a lifeline to people who might otherwise be doomed to endless despair" (Lozano and Mayberg 2015)	

Appendix B – General Questions of the Interviews

This overview is a representation of the questions used in the different interviews. However, the questions were partly different between the actors included in the interview. The questions were reconsidered in advance of each interview, with the particular actor and information gained in previous interviews in mind.

General Questions

- Could you shortly introduce yourself?
- Are you involved with the treatment of patients with depression? If yes, can you tell something about the disorder and the patients? Can you outline the treatment procedure of patients with depression?
- Are you known with Deep Brain Stimulation as a treatment for depression? If yes, can you tell something about the use?
    - When and how were you introduced to this technology?
    - If using, why did you start using DBS as a treatment for depression?
    - What are your expectations considering this treatment?

Technological feasibility

After some general question I will continue with the more technological aspect, the current devices used as well as the possible improvements and current developments.

- How do you see the current development of DBS as a treatment for depression?
- What is the used procedure of the treatment with depression? Who is responsible for which part of the procedure? (who, when, where, how?)
- When DBS is used, to what extent is the protocol you apply comparable to other hospitals (including patient selection and procedure)? If there are differences, what is your opinion about this, how do you consider these controversies?
- What are the main technological difficulties in the application of DBS for depression? (electrodes, battery, brain region, patients?)
    - Is it plausible that these difficulties would hold up the introduction of DBS?
    - Do you have an idea to overcome these difficulties? Is it plausible that engineers will overcome the difficulties?
- How does the application of DBS for depression relate to other technologies under development (like TMS)? Is there a possible competition in experiments, developments or something else?
    - Which technology requires extended development in your opinion? Which technology is the most plausible to become used in the future in the treatment of depression?

Social usability

This part consists of several questions about the use and possible embedding of the technology. I will investigate the current care as well as the possible practices with DBS for depression.

- What is the current procedure to diagnose and treat depression?
    - Which therapy is chosen in most cases? Why?

- Which circumstances might lead to a treatment with DBS?
    - Which patients are currently included in the procedure? How do we determine this and by whom?
    - Might this selection of patients change in the future? How and what will differ?
- Do you consider DBS as a beneficial treatment for patients with depression? Why?
    - Do others (physicians, engineers, patients) probably share this opinion with you? What is the vision of patients who were already included in the experimental phase? Do you have any sources for this or is it mainly based on your own experience?
    - Which factors or persons could influence the guidelines for the embedding of DBS in the current treatment?
- Can evidence-based effectiveness lead to an unproblematic embedding in the psychiatric care? Where and by whom will the treatment be performed?
    - Which possible problems or difficulties do you recognize already?
    - Can the embedding of DBS result in a shift of the current care?

Desirability

After questioning the technology and social implications I will continue with several questions considering the desirability of DBS for depression to investigate the plausibility that it might become a desirable treatment option.

- What consequences would DBS for depression introduce on for example the life of the patient or in society? (In case of discussion about positive consequences only, try to question the less desirable consequences as well)
    - Do you consider these consequences desirable?
- To what extent will different actors consider DBS as a promising desirable technology which we should accept?
- To what extent might DBS replace current treatment options? Do you consider this as desirable? Why?
- Which conditions should become included in the DBS treatment before the medical field will consider it as beneficial?
- Do you think that patients see DBS as a promising desirable technology?
    - Why would they or why would they not?
    - Can you think of objections patients could have?
- One of the discussions considering DBS for Parkinson's Disease is personality change. Do you consider this as a problematic issue concerning DBS for depression? Why?
    - Do you recognize certain other ethical implications for the acceptance of DBS for depression?

Closing questions

Finally I will end with short questions to end the interview

- How do you reckon DBS as a 'normal' treatment option for patients with depression? And do you consider this as desirable?
- Do you have anything to add to this interview?
- Do you have any suggestions who I should interview next? (developers, physicians, patients, organizations, etc.)
- Would you prefer to receive the thesis when finished?