Deep Brain Stimulation Improves Brain Efficiency in Essential Tremor Patients

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DEEP BRAIN STIMULATION IMPROVES BRAIN EFFICIENCY IN ESSENTIAL TREMOR PATIENTS

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The movement disorder essential tremor can be treated with deep brain stimulation (DBS), where electric current is delivered to deep brain structures through permanently implanted electrodes. In this study, brain activity during working memory performance was measured with functional magnetic resonance imaging in thirteen essential tremor patients with DBS in caudal Zona incerta, a diencephalic nucleus. With active stimulation less exertion of certain working memory areas was required to achieve the same level of performance in a manipulation and a maintenance-type working memory task. At the same time, a relatively higher activation was reached for the more demanding manipulation task. These results indicate that DBS can make the brains of tremor patients more efficient in working memory tasks, in accordance with the "efficiency hypothesis" proposed by Nyberg et al. (2014).


Electrical stimulation of deep structures in the brain has been used since the 70's to treat a large variety of conditions, clinically or experimentally. These include chronic pain, obsessive-compulsive disorder, depression, epilepsy, Tourette's syndrome, obesity and vegetative state (Chen, Xiong, Xu & Liu, 2012). Most established, however, is the use of deep brain stimulation (DBS) for treating movement disorders such as Parkinson's disease and essential tremor.

Deep brain stimulation is achieved by inserting a thin, flexible electrode through a burr hole in the skull. From the electrode's exit point in the skull a wire extends under the skin to a neuro-pacemaker placed by the collar bone (Georgi, Stippich Tronnier & Heiland, 2004; Hubble et al., 1996). Each electrode has several (usually four) contacts whose stimulation parameters can be adjusted using an external unit (Medtronics, 2015). The target area is most often situated in the thalamus or basal ganglia, for example the subthalamic nucleus (STN), internal globus pallidus (GPI) or nucleus accumbens (Chen et al., 2012; Gubellini, Salin, Kerkerian-Le Goff & Baunez, 2009).

Even though DBS treatment has often proved highly successful, not least for movement disorders, the exact mechanisms by which the effect is achieved are largely unknown (Chen et al., 2012; Gubellini et al., 2009; Miocinovic, Somayajula, Chitnis, & Vitek, 2013). DBS affects both afferent and efferent axons and fibres, thereby having an influence on brain activity far beyond the locus of stimulation
Electric stimulation of neural tissue also affects astrocytes and neuron cell bodies (Chen et al., 2012), and DBS has been shown to induce a global increase in cerebral blood flow (Mubeen et al., 2017; Sidtis et al., 2012). All these effects depend on the amplitude and frequency of the stimulation (Chen et al., 2012).

**Essential Tremor**

Essential tremor (ET) is a progressive neurological disease, primarily causing motor symptoms in the form of action tremor in both arms (Deuschl, Bain & Brin 1998). More recently it has been shown that cognitive functions are also affected (Chandran & Pal, 2012; Chunling & Zheng 2016; Benito-León 2014; Janicki, Cosentino & Louis, 2013; Louis & Vonsattel, 2008; Passamonti, Cerasa & Quattrone 2012; Passamonti et al., 2011). It is the most common movement disorder in adults and affects around 0.9 % of the general population, with prevalence as high as 4.6 % in persons above 65 years of age (Louis & Ferreira, 2010). It is considered benign, but the motor symptoms can be disabling. The cognitive effects are usually mild and include frontal/executive dysfunction, forgetfulness, and sometimes impairment in verbal memory and visuospatial processes (Chandran & Pal, 2012; Benito-León, 2014).

Anatomically, the condition is typically associated with decreased cerebellar volume and with cell death, particularly of Purkinje cells in the cerebellum but also of other neurons in parts of the cerebrum (Chandran & Pal, 2012; Chunling & Zheng, 2016; Benito-León, 2014; Klaming & Annese, 2014). A smaller subset of patients instead exhibit a presence of Lewy bodies, normally associated with Parkinson’s disease and dementia, in the locus coeruleus in the brain stem (Chandran & Pal, 2012; Benito-León, 2014; Klaming & Annese, 2014; Louis et al., 2007; Louis & Vonsattel, 2008). The more common form is characterised by both a degeneration of the cerebellum and increased cerebellar activity (Chandran & Pal, 2012; Louis & Vonsattel, 2008). The apparently contradictory combination of degeneration and excessive activation can be explained by, among other things, compensatory action and the death of inhibitory Purkinje cells (Louis & Vonsattel, 2008). Compared to healthy controls, ET patients often exhibit altered cortico-cerebellar circuits (Chandran & Pal, 2012; Chunling & Zheng, 2016; Fang et al., 2015) and this has been suggested to account for the cognitive impairments (Cerasa et al., 2010; Chandran & Pal, 2012; Passamonti et al., 2011).

**Deep Brain Stimulation for Essential Tremor and the Zona Incerta**

Patients suffering from medication resistant essential tremor have been receiving DBS treatment since the mid 90’s (Blond et al., 1992; Hubble et al., 1996). DBS treatment for essential tremor has been highly effective, with symptom improvements of 50-95 % (Chopra, Klassen & Steed, 2013; Flora, Perera, Cameron & Maddern, 2010). As with DBS in general, the exact reasons for this are still unclear (Chen et al., 2012; Chopra et al., 2013; Elble, 2014; Miocinovic et al., 2013; Xie et al., 2012). As DBS implantation has replaced the previous procedure of lesioning the same brain targets, the effect has been assumed to be explained by functional inhibition (Miocinovic et al., 2013). Nevertheless, studies have found an increase in output from the stimulated areas (Miocinovic et al., 2013) and DBS is known to work
on synapses to induce a release of neurotransmitters from local efferent excitatory neurons (Chen et al., 2012). Likely the effects are highly complex and involve both inhibition and excitation (Chen et al., 2012; Gubellini et al., 2009; Miocinovic et al., 2013). Regardless of the exact mechanisms, it seems that the DBS overrides the pathological neuronal activity otherwise present in ET and thereby lessens symptoms (Chen et al., 2012; Chopra et al., 2013; Miocinovic et al., 2013).

The most common DBS target for treating ET is the ventral intermediate nucleus of the thalamus (Vim). More recently, another electrode placement has been favoured, namely in caudal Zona incerta (cZi) in the posterior subthalamic area (Chopra et al., 2013; Fytagoridis, 2012; Sandvik, Koskinen, Lundquist & Blomstedt, 2012; Xie, Bernard & Warnke, 2012). An investigation into the optimal location of DBS in essential tremor treatment has shown that of the contacts yielding substantial tremor reduction, a majority were in the posterior subthalamic area and only a minority in the Vim (Sandvik et al., 2012). Indeed, it seems that many of the successful Vim placements are in fact working through stimulation of the nearby Zona incerta (Sandvik et al., 2012). Literally meaning “the zone of uncertainty”, the Zona incerta is a neuroanatomically diverse, elongated nucleus in the diencephalon roughly between the subthalamic nucleus, the medial lemniscus and the red nucleus (Fytagoridis, 2012; Mitrofanis, 2005). It is widely connected to most parts of the central nervous system, including the thalamus, cerebellum, cerebral cortex, reticular activating system and brain stem motor nuclei (Chopra et al., 2013; Mitrofanis, 2005). While its caudal part seems to play a role in the motor system, other areas are associated with functions such as arousal, attention and visceral control (Mitrofanis, 2005). The different subsectors of Zona incerta communicate with each other both within and across hemispheres, meaning that stimulation of either cZi can influence various aspects of brain activity in both hemispheres (Mitrofanis, 2005). Because of the wide connectivity and diversity of functions of Zona incerta, Mitrofanis (2005) points out that one should not be expecting changes in the motor system only when stimulating the cZi.

**Cognitive Effects of Deep Brain Stimulation**

Both negative and positive cognitive and emotional side effects have been reported for DBS treatment. In general, mood and overall quality of life is improved with DBS (Combs et al., 2015; Eisenstein et al., 2014; Houeto et al., 2006; Lewis et al., 2015; Wang et al., 2016) but severe negative effects have been reported, including hypomania, depression, apathy, panic, impulsivity, anxiety, emotional reactivity, pathological gambling, hypersexuality, hallucinations and even suicide (Chen et al., 2012; Dormont et al., 2010; Gubellini et al., 2009; Voon, Kubu, Krack, Houeto & Tröster, 2006). Other factors concurrent with the DBS treatment, such as changes in medication, probably contribute to these effects.

Personality change is a rather common effect of STN DBS. In a study of 27 Parkinson patients a proportion of 22 and 50 per cent of patients and caregivers, respectively, experienced some level of personality change (or “different awareness of life”) in patients one year after operation (Lewis et al., 2015). Both Zona incerta, STN and GPi DBS of patients with Parkinson’s disease have also been associated with weight
gain (McClelland, Bozhilova, Campbell & Schmidt, 2013; Sundstedt et al., 2017), possibly because of coincidental stimulation of hypothalamic satiety centres (McClelland et al., 2013).

Most research on DBS, including cognitive outcomes of the treatment, has been based on Parkinson’s patients with STN stimulation. According to a review by Voon et al. (2006), cognitive effects of DBS in this group are mild or inconspicuous and, when evident, go in both directions. Studies included in the review have found deteriorations in verbal fluency, verbal memory, visuospatial memory, processing speed and some measures of executive function such as response inhibition. Improvements have been found in mental flexibility, working memory, random number generation, processing speed, conceptual reasoning, problem-solving and overall cognitive function. A recent meta-analysis of STN DBS effects on executive function including working memory (Martínez-Martínez, Aguilar & Acevedo-Triana, 2017) report a general reduction of executive functions after DBS surgery compared to before. However, they point out that the lack of placebo or control groups often makes it hard to draw any firm conclusions. In two meta-analyses comparing STN and GPi DBS effects on cognition (Combs et al., 2015; Wang et al., 2016) again small declines in psychomotor speed, memory, attention, verbal fluency, executive function and overall cognition following DBS were reported, with less decline in GPi DBS compared to STN.

The majority of the investigations of DBS and cognition compare performance pre-vs. post-surgery rather than with stimulation on vs. off, introducing a number of possible confounders. The first study to compare cognitive performance with DBS on vs. off was performed by Jahanshahi et al. in 2000. They found improved performance and reduced response times over a number of executive tasks with DBS on rather than off for both STN and GPi patients. At the same time, performance was worse with DBS on in two tasks; a visual learning task for both groups and random number generation for the GPi group. The STN group generally improved more than the GPi group. This study also found a correlation between motor symptom and cognitive improvements with DBS.

One of the most consistent findings in studies of STN DBS and cognition appears to be a worsening of verbal fluency, as reviewed by Højlund, Petersen, Sridharan and Østergaard (2017). It is unclear whether this is due to stimulation or surgery; those few studies comparing DBS on vs. off have found no effect on verbal fluency (Højlund et al., 2017). In a study of thalamic DBS in ET patients by Pedrosa et al. (2014), there was no effect of stimulation on performance in verbal fluency, Stroop or a digit span-task between on and off, but verbal fluency was worse with high-frequency compared to low-frequency stimulation. In one of the very few studies touching upon cognitive effects of cZi DBS in essential tremor, Fytagoridis et al. (2013) found a small but significant decline in verbal fluency three days after operation, before stimulation onset. Such a decline was no longer significant at the group level one year post-operatively with the stimulation turned off, but the individual variation was large. Ten patients were also tested with stimulation on one year after operation and no difference in verbal fluency between DBS settings was found.
DBS has rarely been used with the principal aim of improving cognitive function, but there are a few exceptions. In a review article Sankar, Lipsman & Lozano (2014) report results from four studies using DBS to relieve dementia. Stimulation of the fornix and nucleus basalis seems to improve memory and be able to slow the rate of cognitive decline in Alzheimer's patients.

**Magnetic Resonance Imaging and DBS**

Magnetic resonance imaging (MRI) uses magnetic fields to induce and measure certain magnetic properties in atoms of the body, resulting in detailed, three-dimensional images of internal organs. In functional magnetic resonance imaging (fMRI) the most common measure is the blood oxygenation level dependent (BOLD) signal, reflecting oxygen consumption in a certain brain area (Huettel, Song & McCarthy, 2014). The relationship between BOLD “activation” and the underlying neuronal process is not straightforward. It is somewhat delayed and an indirect measure of brain activity, being more dependent on the capillary structure than the neuronal. Moreover, it is hard to say exactly what an increased BOLD response means in cognitive terms. For example, it is not possible to compare absolute signals in two different brain areas in order to say which one is the strongest (Logothetis & Wandell, 2004). Instead, the technique is best used to compare effects of different stimuli, through careful research design, on the neuronal activity in a certain brain area (Logothetis & Wandell, 2004).

Stereotactic MRI is regularly used in DBS patients during the surgery to guide electrode placement, and sometimes post-operatively to confirm it. However, the use of MRI with the system turned on is associated with risk, particularly of heating of the electrodes (Dormont et al., 2010). At least two cases of brain lesions, one leading to reversible dystonia and the other to irreversible hemiparesis, following MRI in DBS patients have been reported (Henderson et al., 2005; Spiegel et al., 2003). A phantom study has shown potential hazards in the form of electrode heating and sparks from a damaged extension cord (Georgi, Stippich, Tronnier & Heiland, 2004). The electrode also spontaneously switched off a couple of times in this study. Up to now, fMRI with active DBS has therefore been performed sparsely. With newer implants and with careful consideration of safety measures, MRI with active stimulation is now considered safe (Dormont et al., 2010; Medtronic, 2015).

**Working Memory Brain Activity**

Working memory (WM) is a vague and broad concept, usually denoting short-term maintenance and/or manipulation of a limited amount of information other than current sensory input (Baddeley, 2003; Cowan, 2008; D'Esposito & Postle, 2015; Eriksson, Vogel, Lansner & Bergström, 2015). Different theories emphasise different processes as contributing to or making up working memory, such as attention, short- and long-term memory, updating and inhibition (Baddeley, 2003; Eriksson et al., 2015; Cowan 2008; Miyake et al., 2000; D'Esposito & Postle, 2015; Ma, Husain & Bays, 2014; Collette et al., 2005). In essence, it seems that those processes collectively referred to as “working memory” are made up by different combinations of sub-processes and networks from time to time (D'Esposito & Postle, 2015;
Eriksson et al., 2015; Fuster, 2009). This means that there is no specific site for WM in the brain. Instead, brain activity during WM tasks is highly distributed and varied: sensory areas that originally received the information to be handled will be activated as well as those parietal and prefrontal cortex areas associated with executive functions and focused attention (Collette et al., 2005; Eriksson et al., 2015; Wager & Smith, 2003). In general, the more demanding a WM task is, the more pronounced the activation of an involved brain area will be. For example, parietal cortex activity increases with increased taxing of WM capacity up to the capacity limit of 3-4 remembered items, and then levels out (Eriksson et al., 2015).

Though the specific contributions of different areas of the prefrontal and parietal cortex are still unclear, there seems to be a lateralisatation so that left parietal and prefrontal cortex (specifically the ventrolateral prefrontal cortex, VLPFC) are more involved in verbal WM tasks and right parietal and prefrontal cortex (specifically the dorsolateral prefrontal cortex, DLPFC) are more involved in spatial WM tasks (Eriksson et al., 2015; Wager & Smith, 2003). In older adults, particularly those that are high-achieving, this lateralisatation is often diminished and bilateral areas are recruited, probably as a compensatory measure (Cabeza 2002; Cabeza et al., 2002). Additional areas such as the medial temporal lobe, basal ganglia (specifically the striatum) and the cerebellum are also often activated during working memory tasks (Buckner, 2013; Eriksson et al., 2015; Lewis, Dove, Robbins, Barker & Owen, 2004). The cerebellum is engaged in reading and language manipulation, executive tasks, attention, spatial and social processing (Stoodley 2012). Some have suggested that the cognitive contribution of the cerebellum works in roughly the same way as does its motor contributions: by allowing repetition and synchronisation of cerebrally initiated processes (Buckner, 2013; Eriksson et al., 2015). Likewise, the mechanisms of the basal ganglia in cognition seem to be analogous to its modulation of motor action (O’Reilly & Frank, 2006). The basal ganglia are believed to support an adaptive gating mechanism, controlling updating versus maintaining of WM content (Frank, Loughry & O’Reilly, 2001). Basal ganglia disturbances, such as the striatal pathologies seen in Parkinson’s and Huntingdon’s disease, often lead to pronounced cognitive dysfunction (Frank et al., 2001; Lewis et al., 2004). This is in contrast to cerebellar pathologies which usually lead to small cognitive impairments, especially in contrast to the large motor impairments (Buckner, 2013; Lemon & Edgley, 2010).

The present study
The hypothesis of this study is that DBS of the cZi in ET patients will also have an effect on working memory, behaviourally and/or in terms of brain activation. This has, to the best of our knowledge, not previously been investigated.

Deep brain stimulation offers a unique way to investigate the workings of the brain. Even so, brain imaging and cognitive studies in an “on vs. off”-paradigm are still scarce. Moreover, cognitive effects of DBS in ET patients or of Zona incerta stimulation in general is not well investigated. As GPi and STN stimulation for Parkinson’s disease show some important differences between them, yet other effects on cognition might well be seen in cZi stimulation.
In one of the few brain imaging studies of cognition and ET, Cerasa et al. (2010) compared ET patients and healthy controls in a Stroop task. ET patients exerted left DLPFC and both inferior parietal lobes to a higher extent when performing at the same level as controls, indicating a higher cognitive effort of the patients. This corresponds to how older adults typically show maximal frontal and parietal response at lower WM demands compared to younger adults (Eriksson et al., 2015; Nyberg, Dahlin, Stigsdotter Neely & Bäckman, 2009; Nyberg et al., 2014). In a consecutive study from the same group, Passamonti and colleagues (2011) used a working memory task known to engage cerebellar circuits (shown by Chen & Desmond, 2005). In this task, requiring maintenance of 1, 3 or 6 letters over a short period of time, patients indeed showed a greater cerebellar response compared to controls despite similar performance.

One of the two working memory tasks used in this study is similar to that used by Passamonti et al. (2011) and so is expected to require cerebellar activity. The paradigm used here, also including a manipulation task, has previously been used in at least three previous studies investigating effects of cognitive disadvantages on working memory performance and brain activity: Chee and Choo (2004) investigated effects of sleep deprivation, Nyberg et al. (2014) studied effects of aging and carrying the Val-158 allele of the catechol-O-methyltransferase (COMT) gene, which is associated with decreased dopamine levels in prefrontal cortex compared to the Met-158 allele, and Rieckmann, Pudas and Nyberg (2017) used this setup in a four year follow-up study of aging and WM in a group of individuals aged 55-80 years. All three studies found that the various cognitive disadvantages had an effect on brain activity during performance of these tasks, thereby offering a useful backdrop to help interpret the effect, if any, of cZi DBS on brain efficiency.

As would be expected, the previous studies show that the more demanding manipulation task elicits more brain activation than the easier maintenance task. This manipulation-specific activity is especially pronounced in the DLPFC but also found in the cerebellum, thalamus and basal ganglia (Chee & Choo, 2004; Pudas, Persson, Nilsson & Nyberg, 2009). But there is more to the relationship between brain activation and cognitive demand; a high activation indicates low efficiency in a simpler task but high efficiency in a more demanding task. For example, Rieckmann et al. (2017) report less manipulation-specific activation in left DLPFC as a result of participants aging four years and Nyberg et al. (2014) report decreased manipulation-specific activation in bilateral frontal and parietal cortex as a result of old age. Nyberg and colleagues refer to this as the “efficiency hypothesis”, according to which individuals with a cognitive disadvantage, such as old age, need to recruit DLPFC and parietal cortex areas maximally already during simpler tasks which precludes reaching even higher levels during a more demanding task. In their words, “dynamic recruitment of the DLPFC depending on task demands might be conceived of as an indicator of a well-functioning brain” (Nyberg et al., 2014, p. 753).

The direction of a cZi DBS effect on WM performance or brain efficiency cannot be presupposed, as the area is unexplored and as the effects of STN and GPi DBS on performance in cognitive tasks are mixed. But given the role of the cerebellum in
WM, the cognitive decline seen in ET patients and the assumption that DBS ameliorates ET motor symptoms through overriding abnormal cerebellar activity, it is reasonable to expect a beneficial effect of stimulation.

Method

Participants
Data was obtained for 14 essential tremor patients with uni- or bilateral cZi DBS implants, eight males and six females with a mean age of 68.9 years ($SD = 8.6$, $n = 13$). Information about the participants, their condition and stimulation parameters was collected and is displayed in Table 1. One participant was left-handed and also the only one with an implant only in right cZi. This person responded with his left hand and so did one other participant due to less severe tremor in the left. Four persons had bilateral electrodes and the remaining unilaterally in the left cZi. Eleven participants were believed to have inherited the disease, and the age of onset varied between early childhood and 67 years of age. The participants had no side effects after adjustment of the stimulation parameters, with the exception of one person who experienced a subjective worsening of memory following the surgery.

Behavioural and brain imaging data had to be excluded for one participant as her performance in the tasks indicated that she had not followed the instructions. For another participant, there was so much head movement in one session that the first 18 volumes had to be excluded. In addition, accuracy data of a third participant was excluded due to a suspected “yes”-button malfunction during his first session, resulting in only correct rejections and misses but no hits or false alarms, while the

Table 1. Participant data including stimulation parameters. ETRS = Essential tremor rating scale. All data from the participant marked in grey had to be excluded.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Handedness</th>
<th>ETRS Off/On</th>
<th>cZi DBS location</th>
<th>Stimulation mode</th>
<th>Frequency (Hz)</th>
<th>Voltage (V)</th>
<th>Pulse (µs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>52</td>
<td>R</td>
<td>116/26</td>
<td>Bilateral</td>
<td>Bipolar</td>
<td>140</td>
<td>2.5</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
<td>57</td>
<td>R</td>
<td>60/8</td>
<td>Bilateral</td>
<td>Monopolar</td>
<td>160</td>
<td>2.3</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>59</td>
<td>R</td>
<td>41/8</td>
<td>Bilateral</td>
<td>Monopolar</td>
<td>130</td>
<td>1.5</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
<td>67</td>
<td>R</td>
<td>41/17</td>
<td>Left</td>
<td>Monopolar</td>
<td>160</td>
<td>1.8</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
<td>67</td>
<td>R</td>
<td>41/20</td>
<td>Left</td>
<td>Bipolar</td>
<td>160</td>
<td>1.8</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>R</td>
<td>35/5</td>
<td>Bilateral</td>
<td>Monopolar</td>
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<td>1.6</td>
<td>60</td>
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<tr>
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<td>R</td>
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<td>Monopolar</td>
<td>140</td>
<td>1.5</td>
<td>60</td>
</tr>
<tr>
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<td>R</td>
<td>96/19</td>
<td>Bilateral</td>
<td>Monopolar</td>
<td>150</td>
<td>1.8</td>
<td>60</td>
</tr>
<tr>
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<td>75</td>
<td>L</td>
<td>60/26</td>
<td>Right</td>
<td>Monopolar</td>
<td>130</td>
<td>2.3</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
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<td>60</td>
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<tr>
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<td>58/28</td>
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<td>60</td>
</tr>
<tr>
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<td>62/21</td>
<td>Left</td>
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<td>160</td>
<td>1.2</td>
<td>60</td>
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<tr>
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<td>R</td>
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<td>140</td>
<td>1.6</td>
<td>60</td>
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<tr>
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<td>R</td>
<td>84/41</td>
<td>Left</td>
<td>Interleaving</td>
<td>125</td>
<td>1.3</td>
<td>60</td>
</tr>
</tbody>
</table>
proportion of correct answers of answers given varied according to task difficulty. Response time (RT) data for this participant was considered representative however, as there was no difference in RT between correct rejections and hits nor between false alarms and misses in the sample as a whole. Thus, RT and brain imaging data was analysed for 13 participants and accuracy data for 12 participants.

**Procedure**
The working memory paradigm used in this study was developed by Pudas et al. (2009), originally adapted from Chee and Choo (2004). It comprises two delayed match-to-sample working memory tasks – Maintenance, requiring maintaining four letters in memory over a short time period, and Manipulation, requiring manipulating and maintaining two letters – and a Control task. All three tasks are described in fig. 1. The idea behind this paradigm is that by subtracting data collected during Control from the other two tasks, only WM-relevant brain activity will remain, and by subtracting data collected during Maintenance from Manipulation, only manipulation-specific brain activity will remain. The use of subtraction is especially warranted in a study such as this one, considering the evidence of a general increase in cerebral blood flow with DBS (Sidtis et al., 2012; Mubeen et al., 2017) that could influence absolute BOLD measures.

The data were collected with a 1.5 tesla (T) Philips Achieva dStream MR scanner at the University Hospital of Umeå, in which the participants solved the tasks after some initial training. The tasks were presented in a blocked design with three successions of the same task type in each block lasting 27 seconds. During a session 18 such blocks, six each of the three tasks, were presented in a pseudorandom order. Before each new block an instruction screen was shown for four seconds. The procedure was repeated during two sessions for each participant – “ON” and “OFF”,

*Figure 1.* The three working memory tasks. In the Maintenance task, the participant is asked to remember four letters without manipulation. After a delay period of 3.5 seconds during which a fixation cross is shown, the participant is presented with a letter and replies as to whether this letter is one of the remembered by pressing a “yes” or “no” button. In the Manipulation task, two letters are presented and the participant is asked to remember the following letters in the alphabet (so that k + b equals l + c). In the Control task only one letter, repeated four times, needs to be remembered. Letters were presented first in upper case and then in lower case in order to decrease reliance on visual memorisation. An instruction screen was shown for 4 seconds before each new block and a fixation cross was shown for 1 second after each probe letter. Image adapted from Nyberg et al. (2014) with permission.
depending on DBS setting – in a counterbalanced design. Each session lasted about ten minutes during which 188 whole-brain volumes were acquired with a repetition time of 3 seconds. Stimuli were presented on a computer screen seen through a tilted double mirror and recorded by E-prime (Psychology Software Tools, Inc., Pittsburgh, PA).

**Analysis of Behavioural Data**

Task performance was measured as accuracy and response time and analysed with IBM SPSS Statistics 24. Accuracy was defined as the number of correct answers out of the maximum possible of 18 for each of the three tasks – that is, an omitted answer was considered an incorrect answer. Effects of DBS setting (ON or OFF), session order (ON first or OFF first) and task (Manipulation, Maintenance or Control) was investigated with an ANOVA for each performance measure. If such effects were found paired *t*-tests were performed. Statistical significance level for these analyses was set to *p* < .05.

**Analysis of Brain Imaging Data**

fMRI data were processed, analysed and tested with Matlab R2014b (Mathworks Inc., Natick, MA) using DataZ, courtesy of Micael Andersson, an in-house developed extension for SPM (Wellcome Department of Cognitive Neurology, London, UK). Before analysis, the data were preprocessed with slice timing correction, movement correction with unwarping, realignment to the first image of each time series, DARTEL normalisation, smoothing with a 10 mm Gaussian kernel and alignment to Montreal Neurological Institute (MNI) standard space. The initial voxel size was $3.44 \times 3.44 \times 4.40$ mm and the final $2 \times 2 \times 2$ mm.

The data were scanned for head movements after realignment. When movements beyond ~ 2 mm were seen between volumes, these were linearly interpolated to the nearest non-affected volumes using ArtRepair toolbox for SPM (cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). This was done for five time series stemming from four participants.

Statistical analysis was performed with *t*-tests in Matlab on a voxel-by-voxel basis. Contrast files were created for each of the tasks between DBS settings and between tasks within setting, and three task × setting interaction contrasts were created by combining the two factors. This was done first for each individual and then on the group level. The significance threshold for tests of these contrasts was set to *p* < .0001, uncorrected for multiple comparisons, with a minimum cluster size of 10 voxels. Session order was included as a covariate in the group analysis. Contrast values were imported to SPSS for visualisation and further analysis.

In MR-imaging of persons with DBS implants, there is some signal loss in a small area around the electrode and lead and a larger area around the extension cord junction due to hardware interfering with the magnetic fields (magnetic susceptibility artefacts; Georgi et al., 2004). In this study there was signal loss at the group level in parts of bilateral angular and supramarginal gyri, posterior parts of superior, middle and inferior temporal gyri and a small part of the right middle
frontal gyrus (fig. 2), with more extensive loss in the left hemisphere as more participants had the extension cord on that side. Left hemisphere signal loss extended to parts of lateral occipital cortex and pre- and postcentral gyri.

**Ethical Considerations**

The study was ethically approved by Umeå Regional Ethical Review Board, dnr 2011-302-31M. Special precautions were taken in consideration of the risks associated with MRI of DBS patients, such as the use of a head-only transmit and receive coil and a lower field strength (1.5 T rather than the more common 3.0 T). All participants gave their written informed consent. Concerning the literature study, I have tried to avoid using sources that rely heavily on research performed on nonconsenting subjects. Regrettably, both MRI and DBS have been developed by remorseless use of sentient non-humans. Notwithstanding the usefulness of these techniques in treating neurological disease and acknowledging that vivisection likely has hastened this development, abusing members of other species for research is ethically unjustified.

**Results**

**Behavioural Data**

The accuracy for the three tasks was 93/95 % (OFF/ON) for Maintenance, 81/71 % for Manipulation and 97/97 % for Control (fig. 3a). Response times ranged between 0.48 and 3.39 seconds (fig. 3b). Individual median RTs over task repetitions were used rather than means as they are less susceptible to extreme values (Whelan, 2008). For statistical testing, RT data was LN-log transformed to achieve normality.

A three-way ANOVA with the factors session order, DBS setting and task (2 × 2 × 3) and participant as a covariate showed no significant effect of DBS setting on accuracy or RT, neither overall nor within any of the tasks (all $p > .13$; fig. 3a-b). There was a tendency toward a significant interaction effect of session × setting on RT over all three tasks ($F (1, 12) = 2.96$, $p = .090$, $η_p^2 = .04$). This tendency was
Figure 3. Behavioural results for the two WM tasks and the Control task. White bars = DBS OFF, grey bars = DBS ON. Error bars denote +/- 1 standard error. a) Group mean accuracy (correct answers, maximum possible 18) over 12 participants. No difference between DBS settings was significant. b) Group mean response time (s) over 13 participants. No difference between DBS settings was significant. c) Interaction effect of DBS setting and session order on response time for the Maintenance task. The interaction effect was significant at $p = .044$, but the difference between settings or sessions was not.

explored further which revealed a significant session × setting interaction for Maintenance ($F (1, 4) = 4.59, p = .044, \eta^2 = .18$), as depicted in fig. 3c. Independent t-tests revealed no significant differences between settings or sessions (all $p > .35$), but the pattern indicates that starting the first session with DBS off led to longer response times. It is worth noting that only 6 vs. 7 participants took part in each session × setting condition. Session order by itself did not significantly influence either of the performance measures (all $p > .14$). Task, on the other hand, strongly influenced both accuracy ($F (2, 12) = 27.99, p < .001, \eta^2 = .55$; fig. 3a) and response time ($F (2, 12) = 29.53, p < .001, \eta^2 = .60$; fig. 3b), as would be expected. Paired t-tests revealed significant (all $t > 3.3, p \leq .007 d > 1.3$) differences in accuracy between Manipulation-Control and Manipulation-Maintenance within each DBS condition. Response times also differed between the Control task and each of the other tasks in both conditions (all $t > 6.3, p < .001, d > 1.3$), and there was a tendency towards a difference between Manipulation and Maintenance in the OFF condition ($t (12) = 2.01, 95\% CI [-0.01, 0.18], p = .067, d = 0.47$) but not in ON ($t (12) = 0.05, 95\% CI [-0.11, 0.11], p = .959, d = 0.13$).

Brain Imaging Data
In order to verify agreement with previous studies using the same paradigm (Chee & Choo, 2004; Nyberg et al., 2014; Pudas et al., 2009), differential activation between tasks within each DBS condition was tested. As expected, the more demanding task showed a stronger BOLD response compared to the easier task in both OFF and ON, and this activation was mostly located to typical working memory areas (fig. 4). For both Task > Control contrasts in both settings (fig. 4a-d) and for Manipulation > Maintenance in ON (fig. 4f), this included the cerebellum. The opposite direction of activity increase was found only for Maintenance > Manipulation in both settings in occipital areas, probably explained by the increased visual load for the Maintenance task (four letters compared to two).
Figure 4. Between-task t-tests of BOLD response at the group level, \( p < .0001 \), with DBS turned OFF and ON, respectively. Maintenance > Control in blue, Manipulation > Control in green and Manipulation > Maintenance in red. The more demanding tasks consistently show increased activation compared to the less demanding tasks in parietal and frontal cortex areas within both DBS settings.

The contrasts depicted in fig. 4 give the impression of an effect of DBS so that there is less activation in ON than OFF for both Manipulation and Maintenance (with Control subtracted) but more activation in ON for Manipulation compared to Maintenance. To determine if there was indeed such an effect, interaction of task and DBS was tested with t-tests. The tests were restricted with masking to the regions showing significantly more activation for Manipulation than Control in OFF at \( p < .0001 \) (fig. 4c), as this contrast make up a broad working memory network likely to contain most of the relevant activation. Within this network, a significance threshold of \( p < .01 \) (uncorrected) was chosen, as the problem of multiple comparisons is smaller when analysis is performed in a restricted area. Minimum cluster size was still set to 10 voxels.

For the contrast Maintenance > Control within this mask, there was an interaction with DBS in nine clusters in left frontal and parietal lobes (table 2; blue in fig. 5a+c), for example in DLPFC, VLPFC, frontal pole, anterior cingulate cortex, intraparietal sulcus and precuneus. All of these clusters followed a pattern so that the difference between Maintenance and Control was larger in OFF compared with ON, i.e. the working memory-taxing aspect of the Maintenance task elicited more activation in OFF than in ON (fig. 5d+e) and there was no significant interaction in the opposite direction. For the contrast Manipulation > Control, there was an interaction effect in only one cluster in the left intraparietal sulcus, overlapping with a cluster found in the Maintenance > Control interaction (table 2; green in fig. 5a+c). The direction of the interaction for this cluster was the same as above: DBS significantly decreased activity in this area (fig. 5d) and there was no significant interaction in the opposite direction. For the contrast Manipulation > Maintenance there was a significant interaction with DBS in six clusters in the left frontal and right parietal lobe (table 2; red in fig. 5a-c). Here, the difference was instead larger in ON for all clusters. These
findings overlapped with a cluster from the Maintenance > Control interaction in left VLPFC (fig. 5c; contrast values in fig. 5e). Thus, the impression from fig. 4 was confirmed: whereas absolute activation was lowered with stimulation for each of the two working memory tasks compared to Control, the difference in activation between Manipulation and Maintenance increased.

As the influence of DBS on brain activity is to a large extent unknown, it was considered to be of interest to also test interaction effects of task and DBS outside of the working memory network. Such tests were performed in the same manner as above, but without masking and at the decided significance threshold for whole-brain analysis, $p < .0001$. Here, the Maintenance > Control contrast was affected by
Table 2. Locations of significant clusters from the WM network (fig. 5) and whole-brain (fig. 6) analyses of interaction of task and DBS. For Maintenance > Control, all clusters show higher activity in OFF. For Manipulation > Control, the cluster found in the WM network analysis show more activity in OFF but the clusters in the whole-brain analysis show more activity in ON. For Manipulation > Maintenance, all clusters show higher activity in ON, † denotes clusters with a negative difference in OFF (one-sample t-test, p < .05.) * and + denote overlapping clusters. BA = Brodmann area. x, y, z = coordinates of cluster peaks in MNI space.

<table>
<thead>
<tr>
<th>Interaction</th>
<th>WM network (p &lt; .01)</th>
<th>Whole brain (p &lt; .0001)</th>
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<td>Postcentral s.</td>
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DBS only in one cluster in the left frontal cortex (table 2; blue in fig. 6a) such that the difference was positive in OFF but negative in ON (fig. 6g). The Manipulation > Control contrast differed between DBS settings in two clusters located in parietal cortices (table 2; green in fig 6a-b) but here the direction of interaction was the opposite: the difference was negative in OFF but positive in ON (fig. 6g). A more extensive interaction effect was seen for the contrast Manipulation > Maintenance with differential activation in twelve clusters, mainly in the right parietal lobe but also in right hippocampus and left frontal and temporal lobe (table 2; red in fig. 6a-f). A significant effect was also detected in two spurious locations (excluded from fig. 6 and table 2): one in right parietal white matter close to the posterior end of the Sylvian fissure (peak at x, y, z = 44, -40, 28) and one to the right of the right temporal lobe (peak at x, y, z = 68, 4, 2), outside of the brain based on the group mean structural image. All these clusters followed the same pattern of interaction and all but one, the VLPFC cluster also found in the test within the mask, followed a pattern such that the difference was negative in OFF but positive in ON. The contrast values of the most significant cluster in each contrast are depicted in fig. 6g.

The consistent finding that the contrasts were numerically negative in either setting indicates the rather implausible situation where the easier task evokes more brain activity than the harder task. One-sample t-tests were performed to determine if the negative contrast values were significantly different from zero, and they were for six of the Manipulation > Maintenance clusters at p-level .05 (marked with † in table 2).

Because of the signal loss in left parietal cortex (fig. 2) it was suspected that some of the findings in right parietal cortex would be in the lost areas if they were mirrored to the left. Indeed, in the contrast Manipulation > Control in OFF (fig. 4c), used as a mask in some of the analyses, a couple of clusters in the right temporal and parietal lobes were partly in the lost area when flipped to the left. So was some of the parietal activation in the whole-brain Manipulation-Maintenance-DBS interaction. As working memory activation is often bilateral, this implies that there might have been some effect in these areas which was not possible to detect in this study.

**Discussion**

This study showed that brain activity during performance of both Manipulation and Maintenance compared to Control decreased with DBS while performance level was retained. Comparing the two tasks to each other, Manipulation evoked more brain activity than Maintenance and this difference was larger with DBS on than off. It thus seems that when the stimulation is turned on less activation of certain brain areas is needed to achieve the same level of performance, while at the same time higher activation can be reached for the more demanding task. This fits with the efficiency hypothesis, proposed by Nyberg et al. (2014), and indicates that DBS stimulation makes the ET afflicted brain more efficient in working memory tasks. If so, the effect of cZi deep brain stimulation in ET in some respects corresponds to the effect of being younger rather than older (Nyberg et al., 2014; Rieckmann et al., 2017) or having the advantageous Met-158 allele of the COMT gene (Nyberg et al., 2014). The
findings of Cerasa et al. (2010) and Passamonti et al. (2011), where ET patients showed increased brain activity when performing at the same level as controls, lends support to the assumption that while ET lowers cognitive efficiency, cZi DBS restores it. This conclusion rests mainly on the results from the interaction tests within a WM network (fig. 5), while the results of the whole-brain interaction analysis (fig. 6) are somewhat confusing.

For the contrasts between tasks within each DBS setting (as depicted in fig. 4), the findings of this study are largely in accordance with previous studies using the same WM paradigm. Manipulation elicited more activation than Maintenance in left prefrontal cortex both with DBS on and off, as was also found by Chee and Choo (2004), Pudas et al. (2009) and Nyberg et al. (2014). Nyberg et al. (2014) and Pudas et al. (2009) also report results for this contrast in bilateral parietal cortex, right cerebellum (Pudas et al., 2009) and inferotemporal cortex (Nyberg et al., 2014); here, cerebellar and inferotemporal activity was only found in the ON session, while parietal activity was found in both settings but “switched sides” from left in OFF to right in ON (fig. 4e-f). Chee and Choo (2004) found activation in left insula and bilateral thalamus for Manipulation > Maintenance. Effects in the thalamus are also reported by Pudas et al. (2009) along with the caudatus, globus pallidus, anterior cingulate cortex and right precuneus, neither of which was significant for the contrast Manipulation > Maintenance in either setting in this study.

In the interaction tests within the mask, Manipulation > Control and Maintenance > Control both showed decreased activation in an area in the left intraparietal sulcus with DBS switched on (green in fig. 5). The same thing was found in Rieckmann et al. (2017), with the elderly participants of their study being four years younger analogous to DBS on. The left intraparietal sulcus was not differentially affected in the Manipulation > Maintenance contrast in either study. This means that in the left parietal cortex, DBS (and aging) affected the maintenance-aspect of WM that is common to the two tasks but not the manipulation-aspect that sets them apart. The same applies to the areas in left DLPFC and frontal pole where DBS only had a significant effect on the Maintenance > Control contrast (blue in fig. 5).

As for the manipulation-specific activation (red in fig. 5), DBS had an influence in left frontal and right parietal cortex such that there was more manipulation-specific activity in ON than in OFF. This is again in line with findings of Rieckmann et al. (2017). Nyberg et al. (2014) also identified decreased manipulation-specific activation in bilateral frontal cortex as a result of old age and of carrying the Val-158 allele of the COMT gene, and in bilateral parietal cortex as a function of age but not of COMT allele. In the present study, DBS had a significant effect on activity in a cluster in left VLPFC for both the Manipulation > Maintenance and Maintenance > Control contrasts, making it possible to compare the level of activation in an area that is affected by DBS for the maintenance and manipulation aspects of WM separately (fig. 5d). Interestingly, in this area the pattern of activation with DBS turned on reflects the workings of a highly efficient brain, “maximal efficiency” as suggested by Nyberg et al. (2014, p. 753), because Maintenance elicits little more activity than Control while Manipulation elicits a lot more than Maintenance.
Contrary to the above findings, Chee and Choo (2004) observed decreased activation in bilateral parietal regions for both Manipulation and Maintenance after sleep deprivation along with increased activation in left DLPFC for Manipulation but not for Maintenance, conversely to the efficiency hypothesis (if sleep deprivation is to be considered a cognitive disadvantage comparable to for example old age). In their study, Manipulation performance was preserved in sleep deprived participants while Maintenance performance was significantly worse. Chee and Choo suggest that while sleep deprivation has a negative impact on arousal and attention, the more demanding task is able to temporarily increase attention to more normal levels by higher exertion of certain brain areas. If this is the case, such compensation does not seem to be feasible when the cognitive disadvantage consists of old age, carrying the Val-158 allele of the COMT gene – or lack of cZi stimulation in ET.

If DBS indeed induces a general improvement of brain efficiency, a higher manipulation-specific activity in ON would be expected in those areas that are usually involved in the task. From this perspective, the left lateralised findings of the Manipulation > Maintenance interactions with DBS in the frontal lobe are expected, as previous studies have shown increased involvement of the left hemisphere in Manipulation compared to Maintenance (Chee & Choo, 2004; Nyberg et al., 2014; Pudas et al., 2009). Harder to account for are the parietal findings of this interaction, which are completely lateralised to the right (fig. 5). The lack of findings in the left parietal lobe could be explained by a ceiling effect; if this area is already maximally engaged in OFF, there would be no detectable difference in ON. The higher exertion of right parietal cortex in ON compared to OFF could be a result of hemispheric asymmetry reduction, a common finding in older adults hypothesised to compensate for aging effects on the brain (Cabeza, 2002). In the within-setting analyses there is manipulation-specific parietal activation only in the left hemisphere in OFF and only in the right hemisphere in ON (fig. 4e-f), contradictory to a ceiling effect in the left parietal cortex and not supporting asymmetry reduction either, as the parietal activation in ON is still asymmetrical but in the opposite direction. However, DLPFC activation is bilateral in ON but not in OFF (fig. 4e-f), supporting the possibility of compensatory hemispheric asymmetry reduction induced by DBS. As the participants of this study are for the most part above 60 years of age, this might indicate that DBS makes their brain function more similar to that of non-diseased peers.

This interpretation of the apparent asymmetry reduction is complicated by the lack of an increase in performance in the Manipulation task with DBS; though neither is significant in the ANOVA models, there is a tendency toward an improvement in response time but a decline in accuracy (fig. 3a-b). Cabeza et al. (2002) found that when performing at a comparable level, young adults engage DLPFC unilaterally and older adults bilaterally, whereas brain activity of low-performing older adults was unilateral and thus similar to that of younger. Some performance improvement would therefore be expected with bilateral activity in these older adults – unless it is a compensation for a cognitive disadvantage. Thus, the DLPFC asymmetry
reduction and the increase in Manipulation-specific activity in right parietal cortex might alternatively be interpreted as stimulation “making the brain older”.

In the whole-brain analysis there are some rather unexpected findings. Several of the clusters in the Manipulation > Maintenance contrast show a negative difference in OFF (fig. 6g); that is, Maintenance evoked more activity than Manipulation. This can be interpreted as a pronounced inefficiency: when performing the more demanding Manipulation task without stimulation, participants are unable to recruit brain areas to even the same level as when performing the easier Maintenance task. In that case, it is unclear by which means the performance in the task was upheld in OFF. On top of this, a large proportion of the findings are located in the postcentral gyrus (fig. 6b). This is puzzling as the postcentral gyrus is the site of primary somatosensory cortex, not normally associated with cognition. These clusters are both extended and highly significant and cannot be easily dismissed. Furthermore, the contrast Manipulation > Control at the whole-brain level interacts with DBS in the opposite direction compared to within the WM network (fig. 6g vs. 5d); here, the activity is higher in ON than in OFF, inconsistent with the efficiency hypothesis. The most parsimonious explanation for this might be that the two clusters found for this contrast, each of just 12 voxels size, are false positives.

To sum up, the pattern of brain activation during working memory performance with and without stimulation indicates that DBS makes the brains of essential tremor patients more efficient. This effect was most pronounced for a cluster in the left frontal cortex, where DBS affected both the maintenance and manipulation aspects of working memory, and a cluster in left intraparietal sulcus, where DBS affected maintenance only. The findings indicate that with active DBS the brains of ET patients are highly efficient, and hint of the possibility that DBS induces hemispheric asymmetry reduction. An interaction analysis restricted to a working memory network yielded comprehensible results whereas results of a whole-brain analysis at a more rigorous threshold were harder to interpret. Behaviourally, performance was not affected by DBS either in terms of accuracy or response time.

Limitations and Recommendations for Future Studies

The main limitation of this study is its low statistical power as data from only 13 participants were included. This means that the results may be inflated due to false positives and/or that authentic findings are weaker than they would have been given a larger sample size (Poldrack et al., 2017). Moreover, a rather low significance threshold was used, $p < .0001$ in the whole brain and $p < .01$ in the WM network, which is generous as there was no correction for multiple comparisons. The fact that some significant clusters were located outside of grey matter in the whole-brain interaction analysis, along with the other puzzling findings mentioned above, strengthens this suspicion and calls for caution when interpreting the results. On the other hand, the results gain credibility from the good agreement with previous studies in the within-setting, between-task comparisons. With a higher statistical threshold or correction for multiple comparisons, a high rate of false negatives in this small sample would have been expected instead.
Participants were instructed to do their best but not to respond as fast as possible. This might have some relevance for the interpretation of RT measures. Another limitation is the use of a rather low field strength, necessitated for ethical reasons, which gives a lower BOLD signal strength and relatively more noise in the data. Further, the blocked design is limiting as it does not allow for a specific analysis of brain activity during encoding, manipulating/maintaining and response, respectively. However, an event-related design would have entailed even lower statistical power.

The risk of a placebo effect is apparent as the participants were well aware of the current DBS setting. Placebo effects have been shown in DBS for Parkinson's disease (de la Fuente-Fernández, 2004; Mercado et al., 2006; Rätsep & Asser, 2016). Participants might have expected to perform faster or give more accurate responses in either of the DBS conditions which could alter both brain activity and performance. In general, discussion of or control for placebo effects is seldom seen in DBS studies. As the mechanisms of DBS are still rather obscure, this is an important factor to consider.

In future studies, the possibility that DBS somehow facilitates compensation through increased engagement of contralateral areas should be investigated. It would also be interesting to compare resting state activation in ET patients with DBS turned on vs. off. As there is some data showing that ET patients have altered functional connectivity patterns (Chandran & Pal, 2011; Chunling & Zheng, 2016; Fang et al., 2015), it could be hypothesised that DBS might restore resting state functional connectivity to more normal patterns.

In this study it was assumed that brain efficiency was diminished due to ET and partly or fully restored with DBS. But it cannot be precluded that DBS in fact improved brain efficiency beyond this level, not least since the findings indicate “maximal efficiency” in left VLPFC. Therefore, it would be interesting to compare the brain imaging data of this study to that of healthy, age-matched peers. If DBS could indeed improve efficiency beyond the non-diseased level many exciting applications are conceivable, including cognitive enhancement of healthy brains. While such effects have recently been shown for memory encoding with direct stimulation of the medial temporal lobe (Ezzyat et al., 2017), it has not yet been shown for working memory.

References


