

Immediate effects of deep brain stimulation of anterior thalamic nuclei on executive functions and emotion–attention interaction in humans

Kaisa M. Hartikainen^{1,2}, Lihua Sun¹, Markus Polvivaara¹, Maarja Brause¹, Kai Lehtimäki², Joonas Haapasalo², Timo Möttönen², Kirsi Väyrynen², Keith H. Ogawa³, Juha Öhman², and Jukka Peltola²

¹Behavioral Neurology Research Unit, Tampere University Hospital, Tampere, Finland

²Department of Neurosciences, Neurology and Rehabilitation, Tampere University Hospital, Tampere, Finland

³John Magaddino Neuroscience Laboratory, Saint Mary's College of California, Moraga, CA, USA

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Background: Deep brain stimulation (DBS) of anterior thalamic nuclei (ANT) is a novel promising therapeutic method for treating refractory epilepsy. Despite reports of subjective memory impairments and mood disturbances in patients with ANT–DBS, little is known of its effects on cognitive and affective processes. **Hypothesis:** The anterior thalamus has connections to prefrontal and limbic networks important for cognitive control and emotional reactivity. More specifically, anterior cingulate cortex (ACC), linked with ANT, has been assigned roles related to response inhibition and attention allocation to threat. Thus, we hypothesized ANT–DBS to influence executive functions, particularly response inhibition, and modulate emotional reactivity to threat. **Method:** Twelve patients having undergone ANT–DBS for intractable epilepsy participated in the study. Patients performed a computer-based executive reaction time (RT) test—that is, a go/no-go visual discrimination task with threat-related emotional distractors and rule switching, while the DBS was switched ON (5/5 mA constant current) and OFF every few minutes. **Results:** ANT–DBS increased the amount of commission errors—that is, errors where subjects failed to withhold from responding. Furthermore, ANT–DBS slowed RTs in context of threat-related distractors. When stimulation was turned off, threat-related distractors had no distinct effect on RTs. **Conclusion:** We found immediate objective effects of ANT–DBS on human cognitive control and emotion–attention interaction. We suggest that ANT–DBS compromised response inhibition and enhanced attention allocation to threat due to altered functioning of neural networks that involve the DBS-target, ANT, and the regions connected to it such as ACC. The results highlight the need to consider affective and cognitive side-effects in addition to the therapeutic effect when adjusting stimulation parameters. Furthermore, this study introduces a novel window into cognitive and affective processes by modulating the associative and limbic networks with direct stimulation of key nodes in the thalamus.

Keywords: Deep brain stimulation; Anterior thalamic nuclei; Emotion; Executive functions; epilepsy.

Deep brain stimulation (DBS) is an emerging therapeutic method for treating an expanding number of neurological and psychiatric disorders. DBS of bilateral anterior thalamic nuclei (ANT) is a novel

promising therapeutic method for treating intractable epilepsy when epilepsy remains poorly controlled despite antiepileptic medication, and the patient is not eligible for resective surgery (Fisher

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Address correspondence to: Kaisa M. Hartikainen, Behavioral Neurology Research Unit, Finn-Medi 6–7, Pirkanmaa Hospital District, P.O. Box 2000, FI-33520, Tampere, Finland (E-mail: kaisa.hartikainen@uta.fi).

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et al., 2010; Hodaie, Wennberg, Dostrovsky, & Lozano 2002; Kerrigan et al., 2004; Lee, Jang, & Shon, 2006; Lim et al., 2007; Osorio, Overman, Giftakis, & Wilkinson, 2007). ANT-DBS has been CE approved (Conformité Européene) for epilepsy therapy in Europe since 2010.

Knowledge of the basic mechanisms of DBS and of the optimal stimulation parameters is limited. It is thought that DBS disrupts or inhibits epileptiform activity in epileptogenic thalamocortical networks (Lega, Halpern, Jaggi, & Baltuch, 2010; Lim et al., 2008). By targeting crucial nodes in the epileptogenic network, such as ANT with its wide limbic and cortical connections, regions involved in sustaining, propagating, or triggering epileptic activity could be inhibited (Nagel & Najm, 2009; Zumsteg, Lozano, & Wennberg, 2006).

Even less is known about possible side effects of ANT-DBS on cognition and emotion. Optimizing therapeutic effects and minimizing side effects require adjustment of DBS parameters according to knowledge of the therapeutic efficacy as well as the DBS effects on emotion and cognition. In this pursuit, studies on DBS effects on cognition and emotion are crucial. When DBS is used for treatment of neuropsychiatric disorders, the treatment effects reside within affective functions. Thus, developing methods for assessing and understanding the effects of stimulation at different sites of the limbic circuitries is critical.

The significance of the anterior thalamus in cognition and emotion is evident not only due to its anatomical connections between the limbic and associative networks (Kobayashi, 2011; Xiao & Barbas, 2002a, 2002b) but also due to clinical evidence from patients with a single strategic lesion of this structure leading to anterograde and retrograde amnesia, inattention, apathy, and aggression (Lanna et al., 2012; Nishio, Hashimoto, Ishii, & Mori, 2011; Schmahmann, 2003). One of the critical connections of ANT involved in cognition and emotion is the anterior cingulate cortex (ACC; Kobayashi, 2011). The role of the ACC in emotion, attention, and cognitive control is evident from the broad neuroimaging literature (Bush, Luu, & Posner, 2000), as well as neurocognitive studies on patients with ACC lesion (Turken & Swick, 1999). Furthermore, clinical evidence shows that ACC lesion leads to similar emotion- and cognition-related symptoms to those observed in ANT lesion, such as apathy, inattention, and emotional instability (Barris & Schuman, 1953). Specifically, the ACC has been assigned roles in attention allocation to threat (Carlson et al., 2012) and in response inhibition (Braver, Barch, Gray, Molfese, & Snyder, 2001) especially in the context

of emotional stimuli (Albert, Lopez-Martin, Tapia, Montoya, & Carretie 2012).

While ANT stimulation has effects at the target site, it has also been reported to activate distant structures such as the ipsilateral cingulate gyrus, insular cortex, and lateral neocortical temporal structures (Zumsteg, Lozano, Wieser, & Wennberg, 2006). In rats it has been shown that bilateral ANT stimulation, in addition to affecting the metabolism of the target site, modulates energy metabolism in distant regions such as the cingulate and frontal cortex (Gao et al., 2009).

With an effect on associative and limbic structures, ANT stimulation is likely to influence cognitive and emotional functions. In rats, high current ANT-DBS has been shown to impair memory through effects on both local and distant neural functioning (Hamani et al., 2010). In humans, the reported effects of ANT-DBS on cognition and emotion are mixed. Cognitive improvement after long-term ANT-DBS in refractory epilepsy has been reported in a group of nine patients with overall improvement in seizure control (Oh et al., 2012). On the other hand, subjective reports of patients treated with ANT-DBS describe side-effects such as depression and memory impairment (Fisher et al., 2010; Möddel, Coenen, & Elger, 2012).

A myriad of factors influencing mood and cognition in epilepsy patients treated with DBS confound studies on DBS effects on emotion and cognition. Patients receiving DBS treatment for refractory epilepsy are a very heterogeneous group in regard to etiology, seizure burden, medication, level of cognitive abilities, and so on. There are several confounding factors when comparing mood and cognition before and after DBS surgery, including the effect of DBS on seizure burden. The aim of the current study was to investigate the direct and immediate effects of ANT-DBS on affective and cognitive processes in humans, which to our knowledge have not been previously studied.

The insensitivity of the methods used previously contributes to the current lack of knowledge of possible subtle alterations in cognitive and emotional processes due to ANT-DBS. Traditional neuropsychological testing is not suitable for assessing the immediate cognitive and affective effects of stimulating a key node in the associative and limbic networks. Assessing immediate and subtle alterations in the efficacy of higher cognitive control functions—that is, executive functions—and the level of emotional reactivity due to ANT stimulation requires a rapid, easily administered, repeatable, and sensitive method. The computer-based reaction time (RT) test that engages several

executive functions simultaneously—that is, the Executive RT—is such a method (Hartikainen et al., 2010).

The experimental Executive RT test has been developed based on our previous neurocognitive studies employing event-related potential and RT measures in attentional tasks on healthy subjects and patients with frontal lesions (Hartikainen & Knight, 2003; Hartikainen, Ogawa, & Knight, 2000, 2012; Hartikainen, Ogawa, Soltani, & Knight, 2007). The Executive RT test requires multiple cognitive processes to be engaged simultaneously and has been shown to detect subtle executive impairment after mild head injury (Hartikainen et al., 2010). In addition to assessing executive performance, the test taps into emotional reactivity and allows for assessing the emotion–executive function interaction (Hartikainen, Siiskonen, & Ogawa, 2012). Successful performance on this task requires the ability to inhibit prepotent responses and emotional distraction, switching tasks, working memory, and controlled attention.

In the current study, patients with ANT–DBS for treatment of intractable epilepsy performed the Executive RT test while the stimulator was turned on and off. This approach allowed us to compare the immediate effects of DBS stimulation on cognitive performance and emotional reactivity within subjects with control over a variety of factors that have a significant influence on cognition and emotion such as medication, seizure history, severity of illness, mood, and arousal.

Stimulating a key node between the limbic and associative networks is likely to modulate affective and cognitive processes. With DBS influencing neural activity both at the target site and at regions connected to it such as the ACC, we hypothesized ANT–DBS to influence cognitive and affective functions including those assigned to the ACC

such as response inhibition and attention allocation to threat.

METHOD

Patients

Twelve patients (8 male and 4 female; 32.7 ± 9.4 years old) with ANT–DBS treatment for refractory epilepsy participated in this study (Table 1). The testing was carried out an average of 475 ± 216 days after the DBS implantation. One subject was tested two months after the surgery, and the remaining patients were all tested more than six months after the surgery. The study was approved by the Regional Review Board, Tampere University Hospital, Tampere, Finland.

The deep-brain-stimulators were implanted by neurosurgeons in Tampere University Hospital, Tampere, Finland during February 2010 to March 2012. The DBS electrodes (Medtronic 3389, Medtronic, Inc.) were implanted under general anesthesia using a Leksell stereotactic frame (Elekta). Initial stereotactic target was 5–6 mm lateral, 0–2 mm anterior, and 12 mm superior relative to midcommisural point (MCP; Figure 1). Target was then adjusted according to individual anatomy in the 3T magnetic resonance imaging (MRI; Siemens) short tau inversion recovery (STIR) images visualizing the mamillo-thalamic tract and ANT. Postoperatively, the locations of contacts used in the study were determined relative to MCP.

The patient group was heterogeneous in regard to the etiology and type of epilepsy (see Table 1), seizure burden, medication, and cognitive abilities. Based on previous clinical neuropsychological assessment, the cognitive performance varied from widespread cognitive dysfunction with

TABLE 1
Demography of the patients with ANT–DBS implantation

Patient	Sex	Age (years)	Age at diagnosis	Types of epilepsy	Etiology	Imaging findings
1	M	31	11 years	Occipital lobe epilepsy	Cortical dysplasia	MRI+
2	F	27	7 years	Temporal lobe epilepsy	Cortical dysplasia	MRI+
3	F	34	1.5 years	Frontal lobe epilepsy	Cortical dysplasia	MRI+
4	F	32	28 years	Multifocal epilepsy	Post encephalitis	MRI–
5	F	24	16 years	Multifocal epilepsy	Post encephalitis	MRI+
6	M	23	11 years	Multifocal epilepsy	Post meningoencephalitis	MRI–
7	M	48	8 years	Frontal lobe epilepsy	Unknown	MRI–
8	M	25	10 years	Multifocal epilepsy	Post encephalitis	MRI–
9	M	44	7 months	Frontal lobe epilepsy	Unknown	MRI–
10	M	49	12 years	Temporal lobe epilepsy	Cortical dysplasia	MRI+
11	M	24	19 years	Frontal lobe epilepsy	Post encephalitis	MRI–
12	M	31	25 years	Occipital lobe epilepsy	Cortical dysplasia	MRI+

Note. ANT = anterior thalamic nuclei; DBS = deep brain stimulation; MRI = magnetic resonance imaging.

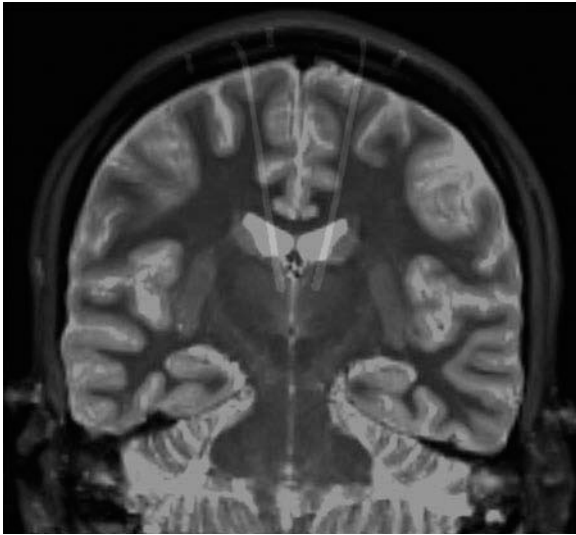


Figure 1. Postoperative computed tomography (CT)-magnetic resonance imaging (MRI) fusion demonstrating a bilateral anterior thalamic nuclei (ANT) implantation, coronal plane.

significant cognitive slowing and executive dysfunction to normal cognitive performance. Some had a history of depression; however, none of the patients had clinical depression during the time of testing.

Executive RT testing

The patients were seated in a sound-attenuated room at a distance of one meter from the computer screen. Electroencephalography (EEG) was recorded while they performed the Executive RT test. EEG results will be reported in a subsequent paper. The Executive RT test is a go/no-go visual attention task with emotional distractors and switching rules for responding. The task was to discriminate triangles pointing up or down. Using their index and middle fingers, the patients pressed a computer mouse button depending on the orientation of a triangle as fast and as accurately as possible after they had seen a go-signal. In the case of a no-go signal, patients had to withhold from responding. A computer program (Presentation, Neurobehavioral Systems, Inc.) presented the visual stimuli and collected the behavioral data.

The test was divided into 32 blocks each lasting 128 s. Each block consisted of 64 two-second trials. After each block, the rule for responding changed, with 20 s allowed for reading the new rule and relaxing between the blocks. A trial started with the presentation of a triangle at the center of the screen for 150 ms. The triangle's orientation was presented randomly. One hundred and fifty milliseconds following the triangle offset, a go/no-go-signal was presented for

150 ms signaling whether to respond or withhold from responding. Each trial lasted two seconds, leaving the subject 1550 ms after the offset of the go-signal to respond before the next trial started. Half of the trials were go-trials, and half were no-go trials. The go/no-go signal was an image resembling a traffic light with three circular spots atop one another on a black background. In each trial, either the topmost or the lowest circle was filled in according to the rule of the traffic lights (topmost red, lowest green). The middle circle was always colored gray. In half of the blocks, a green traffic light signified a go signal and a red light a no-go signal. In the remaining half of the blocks the go and no-go signals were reversed. After each block, the significance of the traffic light changed and thus the rule for responding. Subjects had to hold the orientation of the triangle and the response rule in working memory and flexibly change response sets and inhibit responding according to the previous set. In all trials, a small black line-drawing illustrating a flower or a spider occurred at the center of the middle circle of the go/no-go signal. The line-drawing of a spider was an emotional distractor, while its neutral control image was made exactly of the same physical components but in a different configuration resembling a flower (Figure 2).

DBS stimulation

Monopolar stimulation used in all our patients previously was initially switched to bipolar stimulation in order to prevent the stimulation artifact covering the EEG signal. Furthermore, bipolar stimulation allows for assessing the effects of more focal brain stimulation than monopolar stimulation (Montgomery, 2010), which allows for assessing the effects of more focal brain

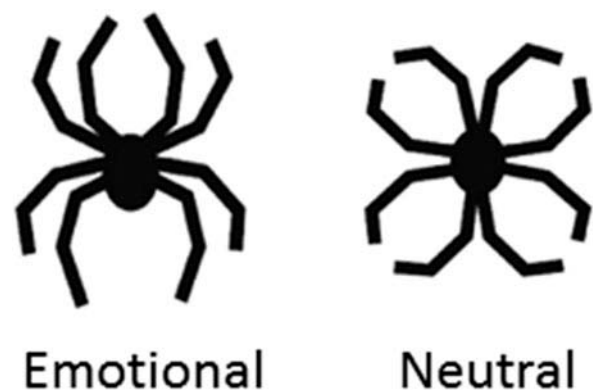


Figure 2. Examples of emotional and neutral distractors. Each distractor is composed of identical elements, which are rearranged to produce either an emotional distractor (spider) or a neutral distractor (flower).

stimulation than monopolar stimulation. In monopolar stimulation the active DBS contact was configured as cathode and the implanted pulse generator (IPG) located subcutaneously below the clavicle as anode. With the bipolar stimulation we aimed to achieve a more focal stimulation than with monopolar stimulation as in addition to the main aim of the study on the general effects of ANT-DBS we also tried to assess whether there were any region-specific effects. A constant current of 5 mA was programmed for all the patients during the study. The stimulation frequency was set at 140 Hz according to the stimulation of the ANT for epilepsy (SANTE) trial (Fisher et al., 2010).

A contact within the ANT in postoperative computed tomography (CT)-preoperative MRI STIR fusion images was selected for stimulating ANT (“at ANT”), whereas a contact most distal to this was selected as a control site (“outside ANT”). These contacts were typically located inferiorly to the ANT within anterior thalamus (see Figure 3). In this study, we defined anterior thalamus as an unspecific area that includes the ANT, medial aspect of the ventral anterior nucleus (VA), the anterior aspect of the dorsomedial nucleus (DM), and white matter between these nuclei, while ANT is a specific identifiable nucleus within anterior thalamus. Consequently, all contacts used in the study were regarded to be located within anterior thalamus, whereas a subgroup of contacts was at the anterior nucleus.

For half of the experiment “at ANT” was stimulated and for the other half “outside ANT,” with the order balanced within the group. The stimulator was turned on every 5 to 6 minutes, allowing each subject to complete two blocks of Executive RT testing, and then turned off for another 5 to 6 minutes, allowing for another two blocks of testing. This was repeated eight times, resulting in 16 blocks (1024 trials) of testing in both on and off conditions in both ANT and outside ANT. The subjects were blind to whether the stimulator was turned on or off and to the position of the active stimulating electrode.

Statistical analysis

The data was analyzed using R (version 3.0.1, the R-foundation for Statistical Computing) with the package ez (Lawrence, 2012; R Core Team, 2013). Repeated measures analysis of variance (ANOVA) was conducted separately for reaction times and for different error types. For reaction time analysis and the different error types the

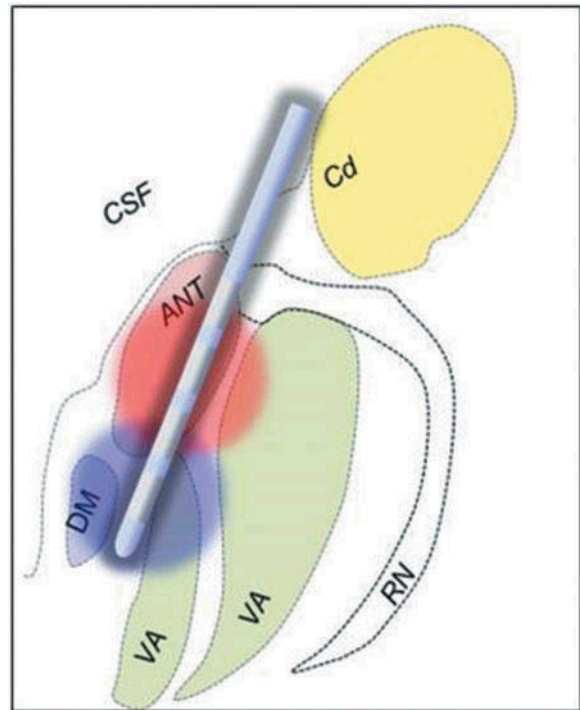


Figure 3. Schematic drawing of deep brain stimulation (DBS) electrode within the anterior thalamus and estimated electric field “at ANT” (red color) and “outside ANT” (purple color), where ANT = anterior thalamic nuclei. Anterior thalamus includes ANT, medial aspect of the ventral anterior nucleus (VA), the anterior aspect of the dorsomedial nucleus (DM), and white matter between these nuclei. The figure also illustrates caudate nucleus (Cd) and reticular nucleus (RN) and cerebrospinal fluid (CSF) in the ventricle. The anatomic structures in this image are modified based on Mai, Paxinos, and Voss (2007).

main factors were stimulation (ON, OFF), location of the active electrode (at ANT, outside ANT), and affective value of the distractor (neutral, emotional). Only RTs to correct responses between 150 and 1000 ms were analyzed. Stimulation-related results are reported with any stimulation-related interaction effect further investigated with post hoc ANOVAs.

There were three different error types—that is, commission errors, incorrect button presses, and missed responses. A commission error indicates a failure to withhold from responding on a no-go trial and is thought to reflect a failure in response inhibition. An incorrect response indicated an incorrect button press on a go-trial in response to the orientation of the triangle reflecting lapse in attention and working memory performance, while a miss indicated failure to respond on a go trial reflecting inattention and/or inability to initiate a response within the allowed time.

RESULTS

There was wide variability in patients' performance levels in the Executive RT test as indicated with an average error rate of $18.5\% \pm 16\%$ varying from 0.44% to 44.6%. The average RT was $527 \text{ ms} \pm 126 \text{ ms}$. There were five patients whose error rates were significantly greater than those of the rest of the patients, with an average error rate of $35\% \pm 7.7\%$ in comparison to an error rate of $6.5\% \pm 4.9\%$ in the other seven patients. Therefore, in addition to the whole group analysis ($n = 11$) we performed a subgroup analysis with patients who were good performers—that is, were able to perform the test with error rate below 15% ($n = 7$). We excluded one patient from the whole group analysis due to not having electrode contacts within the same region used for the “outside ANT” location as that for the rest of the patients. In addition to severe epilepsy, he had a left frontal infarction that further contributed to frontal executive dysfunction and poor performance on the test.

The patients that performed the test with higher error rates all had significant cognitive slowing in previous clinical neuropsychological assessments and signs of executive dysfunction. Four of them lived either in assisted living arrangements or with their parents. None of them were capable of driving, studying, or employment not only due to epilepsy but due to general level of cognitive abilities. One of the patients had frontal lobe epilepsy, and throughout the testing in the EEG recording there were frontal epileptic discharges and many small seizures that impaired his ability to perform the test. As Executive RT test performance relies on the intactness of executive functions, it was expected that executive dysfunction would be reflected in performance level.

RT analysis

Whole group. RT analysis from all subjects ($n = 11$) resulted in a main effect of stimulation, $F(1, 10) = 5.60$, $MSE = 333.3$, $p < .04$, and a main effect of emotion, $F(1, 10) = 5.14$, $MSE = 238.1$, $p < .05$. Stimulation ON slowed RT ($514 \pm 117 \text{ ms}$) compared to stimulation OFF ($504 \pm 113 \text{ ms}$), while emotional distractors slowed down RTs ($513 \pm 116 \text{ ms}$) in comparison to neutral distractors ($505 \pm 114 \text{ ms}$). There was also a significant interaction effect between emotion and stimulation, $F(1, 10) = 1.04$, $MSE = 181.4$, $p < .01$. Post hoc ANOVAs done separately for stimulation ON versus OFF revealed that the main effect of emotion was significant only when the stimulation was

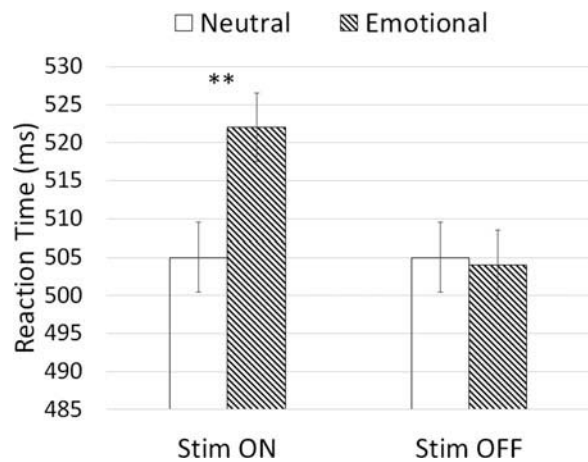


Figure 4. Stimulating the anterior thalamus enhanced attention to threat, as reflected with slowed reaction times (RTs) in the presence of emotional distractors than in the presence of neutral distractors. ANT = anterior thalamic nuclei; Stim = stimulation. $**p < .01$.

ON, with slowed RTs in the context of emotional distractors in comparison to neutral distractors during stimulation (emotional $522 \pm 119 \text{ ms}$, neutral 505 ± 115), $F(1, 10) = 16.63$, $MSE = 185.4$, $p < .003$, but not during stimulation turned OFF (emotional $504 \pm 114 \text{ ms}$, neutral $505 \pm 113 \text{ ms}$), $F(1, 10) = 0.16$, $MSE = 243.1$, $p = .70$ (see Figure 4).

Good performers. RT analysis on the subgroup of good performers ($n = 7$) resulted in a main effect of stimulation, $F(1, 6) = 8.84$, $MSE = 347.3$, $p < .03$, with Stimulation ON slowing RTs ($511 \pm 112 \text{ ms}$) in comparison to stimulation OFF ($497 \pm 104 \text{ ms}$). There was also a significant interaction effect of emotion by stimulation, $F(1, 6) = 12.48$, $MSE = 86$, $p < .02$. Post hoc ANOVAs done separately for stimulation ON versus OFF revealed that the main effect of emotion was significant only when the stimulation was ON (emotional $519 \pm 110 \text{ ms}$, neutral $504 \pm 113 \text{ ms}$); $F(1, 6) = 8.44$, $MSE = 178.7$, $p < .03$.

Error analysis

Commission errors

Whole group. Analysis with all subjects ($n = 11$) resulted in an interaction effect of stimulation and location, $F(1, 10) = 5.96$, $MSE = 0.07\%$, $p < .04$, for commission errors—that is, errors where withholding a response failed. Post hoc ANOVAs carried out separately for active electrode position “at ANT” and “outside ANT” conditions revealed a main effect of stimulation only when the active

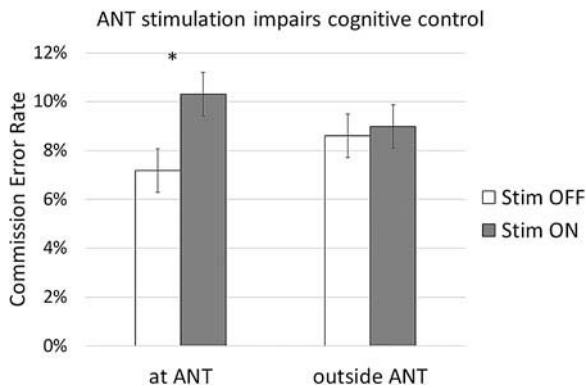


Figure 5. Stimulating the anterior nucleus of thalamus impaired response inhibition, as reflected in increased commission error rate. Stim = stimulation. $*p < .05$.

electrode was “at ANT,” $F(1, 10) = 5.44$, $MSE = 0.20\%$, $p < .05$, with more commission errors made when the stimulator was ON ($10.32\% \pm 9.16\%$) than when it was turned OFF ($7.17\% \pm 8.10\%$). In contrast, the main effect of stimulation did not exist while the active electrode was “outside ANT,” $F(1, 10) = 0.15$, $MSE = 0.11\%$, $p = .71$ (see Figure 5).

Good performers. The interaction of stimulation and location for commission errors did not reach significance in the subgroup analysis of the good performers ($n = 7$), $F(1, 6) = 4.45$, $MSE = 0.07\%$, $p = .08$.

Missed responses

Whole group. There was no significance for miss error rate analysis in the whole group level ($n = 11$).

Good performers. Miss error rate analysis of good performers ($n = 7$) resulted in a main effect of stimulation, $F(1, 6) = 7.04$, $MSE = 0.16\%$, $p < .04$, with stimulation ON increasing miss error rate ($3.79\% \pm 3.03\%$) compared to stimulation OFF ($0.93\% \pm 0.99\%$).

Incorrect errors

Whole group. There was no significance for incorrect errors in the whole group level ($n = 11$).

Good performers. Analysis of incorrect error rate within good performers ($n = 7$) resulted in a main effect of emotion, $F(1, 6) = 16.40$, $MSE = 0.08\%$, $p < .007$, with emotional distractors increasing incorrect error rate ($8.66\% \pm 4.63\%$)

compared to neutral distractors ($5.67\% \pm 3.92\%$). There was no stimulation-related effect.

DISCUSSION

This is the first study to show the immediate effects of stimulating the anterior part of the thalamus, and specifically the anterior nucleus of thalamus, on emotional and cognitive processes in humans. Anterior thalamic stimulation altered emotion–attention interaction and impaired cognitive control. More specifically, ANT–DBS compromised response inhibition and enhanced attention allocation to threat.

Holding a critical position in the “Papez circuit” (Papez, 1937), ANT has connections with the other parts of the limbic system including the ACC. The ACC, on the other hand, has been assigned many different roles related to emotion, attention, and cognitive control (Bush et al., 2000; Dalgleish, 2004; Lane et al., 1998), specifically roles related to response inhibition (Braver et al., 2001) and attention allocation to threat (Carlson et al., 2012). Therefore, we hypothesized ANT–DBS to influence response inhibition and modulate emotional reactivity to threat. Supporting our hypothesis, ANT–DBS resulted in increased commission error rate and increased effect of irrelevant threat-related emotional stimuli on performance speed. The results suggest that ANT–DBS disrupts the function of networks responsible for cognitive control required for inhibiting prepotent responses. Furthermore, the results suggest enhanced allocation of attentional resources to threat-related stimuli due to ANT–DBS.

Preattentive processing of fear-relevant stimuli, such as spiders, as well as automatic attention allocation to biologically threatening stimuli, supports survival and is one of the key functions of the limbic system (Ohman 2005; Ohman, Flykt, & Esteves 2001). In the current study we used line-drawings of spiders to evoke these automatic processes to fear-relevant stimuli. Line-drawings were used in order to allow for full control of low-level visual attributes of the stimuli such as brightness, contrast, and so on. Emotionally neutral control images were constructed of the exact same line-components as the emotional stimuli. Identical low-level visual attributes are unobtainable with most other emotional and emotionally neutral control stimuli, especially with natural scenes or photos. Processing line-drawings of spiders relies on low-spatial-frequency visual information. Low-spatial-frequency fearful faces have been shown to

preferably activate the amygdala in comparison to high-frequency stimuli (Vuilleumier, Armony, Driver, & Dolan, 2003). Furthermore, schematic emotional facial expressions have been shown to evoke amygdala activation (Wright, Martis, Shin, Fischer, & Rauch, 2002). Line-drawings of spiders similar to the ones used in our study have been shown to capture spatial attention in neglect patients possibly due to preserved ventral temporal/subcortical pathways into the amygdala (Vuilleumier & Schwartz, 2001). Thus, in the light of previous literature, the spider stimuli used in this study presumably activate fast, robust, automatic threat-related processes in the limbic system and have privileged access to the attention system.

While it is often adaptive that stimuli signaling potential threat have privileged access to the attention system, failure to filter out irrelevant threat-related information may reflect dysfunctional bias to threat as seen in mood disorders such as anxiety and depression (Leppänen, 2006; Stout, Shackman, & Larson, 2013). Diminished frontal, including ACC, activation has been reported in anxiety and has been suggested to reflect reduced top-down control resulting in attentional bias to bottom up threat-related information (Bishop, Duncan, Brett, & Lawrence, 2004). Disrupting the top-down frontal control mechanisms over the subcortical automatic bottom-up influence could be a plausible mechanism for enhanced attention capture by threat-related distractors due to anterior thalamic stimulation. The enhanced effect of threat-related distractors due to anterior thalamic stimulation observed in this study is similar to attentional bias to unpleasant emotional information seen in mood disorders. On the other hand, depression has been reported as a subjective side-effect of ANT-DBS (Fisher et al., 2010; Möddel et al., 2012)

While it is plausible that a similar disruption of frontal top-down control of irrelevant threat-related stimuli contribute to the enhanced attention allocation to threat due to anterior thalamic stimulation as is seen in mood disorders, the exact mechanisms of the emotion effect remain to be studied. However, a behavioral measure of emotional reactivity will provide an objective way to assess the effect of DBS on emotion systems, not only when modulation of emotion system is part of the side effect profile, but also when modulation of emotion system is the target of the DBS as when used in the treatment of severe depression.

With connections to ACC and orbitomedial prefrontal cortex, ANT has been suggested to contribute to emotional and cognitive control functions (Child & Benarroch, 2013). Thus, both the enhanced emotional reactivity and impaired

cognitive control observed in this study due to ANT-DBS is explicable by connections and functions of ANT and its networks. The increased commission errors due to stimulation showed a location by stimulation interaction effect with post hoc analysis localizing the effect to ANT. On the other hand, the emotion effect was not merely localized to ANT by statistical analysis but to a broader region of the anterior thalamus. The lack of region specificity for the emotion effect may be due to other anterior thalamic structures sharing similar limbic connections and functions as ANT.

The net influence of ANT-DBS on cognitive and affective functions is likely the sum of stimulation effects on different structures in a broader region of the anterior thalamus. While the ANT is the target in treatment of epilepsy, in current clinical practice due to limitations and challenges in imaging and targeting ANT the contact electrodes may sometimes actually be located somewhere in the anterior thalamus in the vicinity of ANT, including the structures we referred to as outside ANT. Furthermore, monopolar stimulation used in the treatment of epilepsy is associated with broader electric field than the bipolar stimulation used in this study. Consequently, in the treatment of epilepsy the other anterior thalamic structures in addition to ANT are likely to be stimulated to some extent as well even when the exact targeting of ANT is successful.

With current challenges in imaging and targeting deep brain structures such as ANT there is a call for other ways than imaging to localize the stimulating electrode. Region-specific behavioral effects might in the future provide behavioral biomarkers for DBS target sites. In addition to investigating more general anterior thalamic stimulation effects, we aimed to assess possible ANT-region-specific effects of DBS. In search for such behavioral biomarkers, we found disruption of cognitive control required for response inhibition to be due to ANT stimulation but not due to stimulating other regions in the vicinity of ANT.

Deficits in executive control functions compromise the efficient use of other cognitive domains and thus often challenge everyday life even if the basic cognitive domains are intact. Traditional neuropsychological testing is not sensitive to subtle deficits in executive functions (Hanna-Pladdy, 2007) or altered emotional reactivity. Unlike traditional neuropsychological testing, the Executive RT test engages several executive functions simultaneously and thus better mimics the everyday life challenges on brain functions. Furthermore, the rapid stimulus presentation allows detection of

temporally limited alterations in cognitive performance, making it suitable for studying the immediate effects of different DBS stimulator settings on rapid mental functions. With a high number of trials in each condition, significant differences may be detected within subjects even when the alteration in cognitive performance level is subtle. Executive RT test requires maintained attention, rapid detection, and responding to stimuli within fractions of seconds and thus makes it also suitable combined with EEG recording for detecting short lapses of attention or consciousness due to a short seizure that would clinically remain unnoticed.

While the results from this study are not directly transferable to the typical clinical situation where a different stimulation cycle is used, our results raise an important issue emphasizing the need to further consider the effects of ANT-DBS stimulation parameters on emotion and cognition. Based on the SANTE trial (Fisher et al., 2010) the recommended stimulation cycle for ANT-DBS in treatment of epilepsy is one minute of active stimulation followed by a 5-min period without the stimulation. In the present study we compared the effects of constant stimulation during the test cycle (5–6 min) with a similar period without stimulation. Furthermore, the net effects of ANT-DBS on cognitive functioning depend heavily on the change in seizure burden most likely explaining the benefits on cognition obtained in a previous study (Oh et al., 2012).

The current results further highlight the need for future studies with sensitive methods and high temporal resolution allowing assessment of rapid and subtle cognitive and emotional effects of electric stimulation of deep brain structures with connection to associative and limbic systems. Whereas the optimal DBS parameters remain to be established, adjusting the parameters requires knowledge not only of DBS effects on therapeutic efficacy but also on its effects on emotion and cognition. Thus, this and similar future studies are critical in developing DBS treatment toward optimal outcomes minimizing side effects.

In conclusion, we found immediate objective effects of ANT-DBS on human cognition and emotion, as evidenced by impaired cognitive control and altered emotional reactivity. The results provides clinical relevance in highlighting the need to consider affective and cognitive side-effects in addition to the therapeutic effect when choosing the optimal stimulation parameters. This study further bears neuroscientific relevance by introducing a novel research approach into studies on emotion systems by modulating the limbic network with direct stimulation of a key node in the thalamus in a conscious human brain.

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