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Human anterior thalamic nuclei are involved in emotion–attention interaction

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ABSTRACT

Patients treated with deep brain stimulation (DBS) provide an opportunity to study affective processes in humans with "lesion on demand" at key nodes in the limbic circuitries, such as at the anterior thalamic nuclei (ANT). ANT has been suggested to play a role in emotional control with its connection to the orbitofrontal cortex and the anterior cingulate cortex. However, direct evidence for its role in emotional function in human subjects is lacking. Reported side effects of ANT–DBS in the treatment of refractory epilepsy include depression related symptoms. In line with these mood-related clinical side effects, we have previously reported that stimulating the anterior thalamus increased emotional interference in a visual attention task as indicated by prolonged reaction times due to threat-related emotional distractors. We used event-related potentials to investigate potential attentional mechanism behind this behavioural observation. We hypothesized that ANT–DBS leads to greater attention capture by threat-related distractors. We tested this hypothesis using centro-parietal N2–P3 peak-to-peak amplitude as a measure of allocated attentional resources. Six epileptic patients treated with deep brain stimulation at ANT participated in the study. Electroencephalography was recorded while the patients performed a computer based Executive-Reaction Time test with threat-related emotional distractors. During the task, either ANT or a thalamic control location was stimulated, or the stimulation was turned off. Stimulation of ANT was associated with increased centro-parietal N2–P3 amplitude and increased reaction time in the context of threat-related emotional distractors. We conclude that high frequency electric stimulation of ANT leads to greater attentional capture by emotional stimuli. This is the first study to provide direct evidence from human subjects with on-line electric manipulation of ANT for its role in emotion–attention interaction.

1. Introduction

Stimulating deep brain structures is an emerging therapeutic method thought to modulate dysfunctional neural circuits underlying many neurological and psychiatric disorders. Limbic and associative circuits important for emotional and cognitive processes play a key role in many neuropsychiatric disorders treated with deep brain stimulation (DBS). However, knowledge on the effects of DBS on these circuits is limited. Deeper understanding of how DBS impacts affective functions is clinically relevant for optimizing DBS parameters, allowing for optimal treatment effect and minimal affective side effects, such as depression related symptoms (Fisher et al., 2010). In addition, DBS studies provide novel insight into the neural circuits behind emotion, attention and cognition in a conscious human brain with electrical stimulation of the key nodes in these circuits. High-frequency electric stimulation used in DBS treatment is thought to mimic a reversible lesion that temporarily disrupts the function of the target nuclei. Thus, invaluable information on emotion, attention and cognition and their interaction in humans is obtained by periodically disrupting and recovering the function of the key nodes in the limbic and associative circuits while brain's electrical responses are recorded in tasks engaging emotional, attentional and cognitive functions.

Stimulation targets used for the treatment of the medically refractory epilepsy include the anterior nuclei of thalamus (ANT). ANT is a suitable DBS target due to its central connectivity and possible role in the propagation and maintenance of seizure activity (Child and Benarroch, 2013; Takebayashi et al., 2007). In addition to its therapeutic effect of reducing seizures, adverse

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effects, such as depressive symptoms, have been reported following ANT–DBS (Fisher et al., 2010; Möddel et al., 2012). In line with these adverse affective effects we have previously shown that stimulating the anterior thalamus enhanced emotional interference of threat-related distractors (Hartikainen et al., 2014).

ANT's role in emotional processing was first introduced by Papez (Papez, 1937) and it is part of the MacLean's limbic system (MacLean, 1949). Since the concept of the limbic system our understanding of the neural circuits underlying emotional processing has evolved significantly (Dalgleish, 2004; LeDoux, 2012), especially in the areas of emotion–attention and emotion–cognition interaction (Hartikainen et al., 2000; Ochsner and Gross, 2005; Okon-Singer et al., 2015; Petersen and Posner, 2012). Recent findings are facilitated by the modern neuroimaging methods and the extensive research especially about the roles of the amygdala and the PFC and the interaction of the various parts of the emotional circuits. However, even if ANT is routinely mentioned in the traditional emotion literature, mostly based on its anatomical connections, its role in emotional processing has remained elusive. This study seeks to fill the gap by taking advantage of the ANT–DBS used to treat refractory epilepsy.

ANT has been suggested to play a role in emotional (Marchand et al., 2014) and executive functions mainly due to its connections with the amygdala (van Groen et al., 1999), orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Child and Benarroch, 2013), but direct evidence from humans for ANT's role in these functions is limited (Bockova et al., 2014; Hartikainen et al., 2014). ANT has major efferent connections to ACC (Xiao and Barbas, 2002) which in turn has extensive cortico-cortical connections with the lateral prefrontal cortex (LPFC) (Paus, 2001). The ACC has been implicated in a wide variety of different motivational, emotional and cognitive functions (Bush et al., 2000), with the dorsal ACC (dACC) identified as playing a key role in cognitive control (Botvinick et al., 2001). A model of dACC function has been suggested describing the role of the dACC as being involved in integrating information for determining and regulating the amount of LPFC cognitive control (Shenhav et al., 2013). Sufficient amount of LPFC cognitive control is required for efficiently inhibiting emotional distraction. Missing or noisy input from ANT to dACC due to high frequency electric stimulation of ANT could lead to inadequate allocation of cognitive control at the LPFC thereby accounting for increased emotional distraction of behaviour during ANT–DBS (Hartikainen et al., 2014).

The efficacy of an intact LPFC and the fidelity of its cognitive control are required when selecting relevant objects for attention while suppressing or filtering out irrelevant ones (Chao and Knight, 1998; Shimamura, 2000). Objects are thought to compete for the brain's limited processing resources. Biased competition theory of selective attention suggests that both task-related top-down and stimulus-related bottom-up biasing mechanisms influence the attentional competition (Desimone and Duncan, 1995). As such, emotional distractors due to their biological and behavioural relevance capture attentional resources (Hartikainen et al., 2000; Ohman et al., 2001; Vuilleumier and Schwartz, 2001). This in turn leads to task interference (Hartikainen et al., 2000; Hartikainen et al., 2010; Hartikainen et al., 2007; Pessoa et al., 2012) and attention network activation (Barcelo, 2009; Jaeger and Rugg, 2012; Maratos et al., 2000; Mäki-Marttunen et al., 2014). Thus, bottom-up influence of emotional stimuli is under top-down frontal control which limits its influence on attention and behaviour when distracting to the current goals. Any perturbation to actively recruit prefrontal control mechanisms can alter normal emotion–attention interaction. Correspondingly, decreased frontal functions may lead to diminished top-down control and consequently enhance the bottom-up influence of negative emotional information. This greater attention allocation to negative emotional stimuli thought to be related to deficient prefrontal control is seen in anxiety (Bishop, 2008), depression (Leppänen, 2006; Matthews and Wells, 2000) and mild traumatic brain injury (Mäki-Marttunen et al., 2015). And similar to depression (Leppänen, 2006; Matthews and Wells, 2000) greater emotional interference by negative emotional stimuli was seen during ANT–DBS as evidenced by prolonged reaction times (Hartikainen et al., 2014).

To investigate whether attentional mechanisms participate in increased emotional interference previously observed with ANT–DBS (Hartikainen et al., 2014) we compared the brain's electrical responses to events, i.e. event-related potentials (ERPs), when this stimulation was on and off. ERPs are well-suited for studying the neural mechanism behind emotion–attention interaction and its alterations resulting from DBS. On the other hand, patients treated with ANT–DBS due to refractory epilepsy provide an opportunity to study ANT's function by periodically disrupting and recovering its function with high-frequency electric stimulation. Targets in attention tasks evoke a positive parietal ERP waveform at about 300–600 ms after the target called P3 preceded by a negative deflection called N2 (Patel and Azzam, 2005; Polich, 2007). In the context of novel (Daffner et al., 1998) or emotional stimuli (Hartikainen et al., 2007) N2–P3 peak-to-peak amplitude is thought to reflect the amount of attention allocation with greater N2–P3 peak-to-peak amplitude reflecting greater attention allocation. Peak-to-peak amplitude measure accounts for possible baseline shifts or slow fluctuations that might contaminate single peak measurements and thus makes it a more robust electrophysiological marker in studies with small patient populations that possess greater variability in ERP waveforms and noisier ERP recordings than healthy subjects. N2–P3 peak-to-peak amplitude has been previously used successfully to detect alterations in emotion–attention interaction in patients with mild head injury (Mäki-Marttunen et al., 2015) and in patients with lesion to the orbitofrontal cortex (Hartikainen et al., 2012). emotion–attention interaction and how it is reflected in N2–P3 amplitude modulation is predominantly observed over the parietal region (Hartikainen et al., 2007; Kayser et al., 1997). In addition, the parietal region is important in P3 generation and in attention in general (Behrmann et al., 2004; Polich, 2007). To that end we used centro-parietal N2–P3 ERP peak-to-peak amplitude as a measure of allocated attentional resources to assess attentional allocation in context of emotional distractors and its alterations due to DBS.

We hypothesized that ANT is involved in emotion–attention interaction and that attentional mechanisms play a role in increased emotional interference previously observed with ANT–DBS. Reflecting greater allocation of attentional resources to threat-related emotional distractors we expected ANT–DBS to result in increased centro-parietal N2–P3 amplitude along with greater behavioural interference in the context of emotional distractors.

2. Material and methods

2.1. Subjects

Thirteen patients with bilateral ANT–DBS treatment for refractory epilepsy participated in the study. The study was approved by the Regional Review Board, Tampere, Finland. The deep-brain-stimulator was implanted in patients by neurosurgeons in Tampere University Hospital.

Seven patients were excluded from the ERP analysis. Five out of the seven patients were excluded due to excessive EEG artefacts or epileptiform activity leading to unidentifiable ERPs. Two patients were excluded due to different anatomic locations of the stimulating/active contacts. Six patients (3 females and 3 males) with the age of 37 ± 13 years old were included in both behavioural and ERP analysis, Table 1. Out of the six patients, four were responsive to the treatment with over 50% reduction of epileptic activity, while two had less than 50% reduction of seizures. None of the 13 patients had previous experience in similar

Table 1
Demography of the ANT–DBS patients.

Patient number	Age/gender	Age at diagnosis (yr)	Types of epilepsy	Aetiology	Imaging findings	Medication
1	31/Male	11	Occipital	Cortical dysplasia	MRI +	Gabapentin
2	27/Female	7	Temporal	Cortical dysplasia	MRI +	Oxcarbazepine, clobazam, zonisamide
4	32/Female	28	Multifocal	Encephalitis	MRI -	Clobazam, zonisamide, lacosamide,
5	24/Female	16	Multifocal	Encephalitis	MRI +	Oxcarbazepine, topiramate, clobazam, levetiracetam,
10	49/Male	12	Temporal	Cortical dysplasia	MRI +	Oxcarbazepine, clobazam, lacosamide,
13	57/Male	15	Multifocal	unknown	MRI −	Oxcarbazepine

MRI=magnetic resonance imaging; '+'=imaging findings; '−'=no imaging findings.

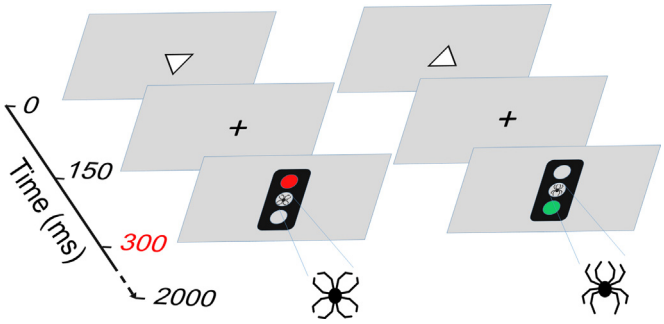

Fig. 1. Schematic presentation of the Executive-RT test. Subjects respond to the orientation of the triangle by a button press in case of a Go-trial indicated by the colour of the traffic light. In the middle of the traffic light there is a task-irrelevant emotional (spider) or emotionally neutral distractor. The emotional and emotionally neutral distractor consist of exactly same line components but in a different configuration. This allows for controlling the physical attributes of the stimuli such as colour, contrast, complexity, etc. Thus, any differences between emotional and emotionally neutral stimuli can be attributed to emotional significance. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

experimental test.

2.2. The Executive Reaction Time Test

Electroencephalography (EEG) was recorded while participants performed the Executive Reaction Time (RT) -test (Hartikainen et al., 2010). The Executive RT-test is a computer-based visual attention task (Fig. 1) requiring multiple executive functions to be engaged simultaneously. Patients sat comfortably in a quiet dimly light room in front of a computer screen and responded with a keypad to visual stimuli according to instructions. Subjects were instructed to stay relaxed, keep their eyes on the location of the fixation cross in the middle of the screen, avoid any unnecessary eye movements or blinks and respond as fast and accurately as possible. The distance from the computer screen was fixed to one meter. Visual stimuli were presented and behavioural data collected with Presentation software (Neurobehavioral System, Inc., Berkeley, CA, USA).

The subject's task was to respond as fast and accurately as possible with a button press to the orientation of a triangle in case of a Go-trial and withhold from responding in case of a NoGo-trial. Each trial starts with a triangle (150 ms) pointing up or down followed by a fixation cross for 150 ms in the middle of the computer screen. Then a Go- or a NoGo-signal is presented for 150 ms indicating whether to respond to the orientation of the previously presented triangle or not. The Go/NoGo signal is followed by a fixation for 1550 ms allowing time for the patient to respond before the next triangle. The Go/NoGo signal is a green or a red traffic light with the rule for responding changing every few minutes. In the middle of the traffic light there is a distractor, which is either neutral (non-threating) or emotional (threat related). Threat related distractor is a line drawing making the shape of a spider and neutral distractor is a line drawing with same elements as control (Fig. 1). The significance of the green and red traffic light changes between each block. In half of the blocks green light indicates a Go trial and red a NoGo trial. In the other half of the blocks this rule is reversed. The direction of the triangle and the Go/NoGo signals are randomized. Dominant hand was used for pressing buttons (patient p10 used left hand; other patients used right hand). A total number of 32 blocks with 64 trials in each block leading to total of 2048 trials per subject were included in the test.

Subject performance in the Executive-RT test is reflected in the speed and accuracy of responses. Different error types reflect failures in different cognitive processes. There were three different error types, i.e. incorrect button press, misses and commission errors. Incorrect button press to the orientation of the triangle indicates lapse in working memory performance. A miss is a failure to respond within the given time indicating a lapse in attention performance. A commission error is a failure in withholding a response during a NoGo trial indicating inefficient response inhibition. In addition to testing efficiency of different cognitive processes, the Executive-RT test with the threat-related distractors allow for evaluating the automatic allocation of attention to threat (Hartikainen et al., 2010; Hartikainen et al., 2012; Hartikainen et al., 2014; Mäki-Marttunen et al., 2015).

2.3. EEG recording and processing

EEG was recorded using a 64-channel actiCAP electrodes (Brain Products GmbH, Germany) with sampling rate of 500 Hz using a common reference. Electrode impedance was kept below 5 kΩ for all electrodes. ERP analysis was conducted with Brain Vision Analyzer2 software (Brain Products GmbH, Germany). At the beginning of the pre-processing EEG was re-referenced to the linked mastoids (Tp9 and Tp10). In order to remove low frequency drifts and high frequency artefacts, such as DBS artefacts, EEG signal was filtered with 0.1–30 Hz band pass filter. Ocular movement artefacts were removed using Independent Component Analysis (ICA), where the EEG was decomposed into independent components using the extended Infomax algorithm. Components corresponding to ocular movement artefacts were identified visually and removed, typically one to two components. The EEG was segmented into 2000 ms segments beginning 200 ms pre-stimulus (triangle) and continuing 1800 ms post-stimulus. Segments were baseline corrected for each trial by setting the average of 200 ms period pre-stimulus to zero. Segments containing activity greater than $\pm 70\,\mu V$ were considered artefacts and rejected. Next, ERPs were calculated by averaging the segments for each condition separately.

Visual inspection of the ERP waveforms showed negative deflection within 200–400 ms after the onset of the traffic lights (Go/NoGo signal) followed by a positive deflection within 300–700 ms corresponding to N2 and P3 peaks. Thus, N2 was defined as the lowest negative peak within 200–400 ms (500–700 ms from the trial onset, i.e. the presentation of the triangle) and P3 as the highest positive peak within 300–700 ms (600–1000 ms after trial onset). The N2 and P3 peaks were detected automatically from each subject's ERP waveforms and visually inspected to confirm correct detection. Final peak value was an average of 20 ms around detected maximum/minimum. Finally, N2–P3 peak-to-peak amplitude was obtained by subtracting N2 peak amplitude from P3 peak amplitude. Regional N2–P3 peak-to-peak amplitude, covering the central (C1, C2, C3, C4, and Cz) and centro-parietal (CP1, CP2, CP3, CP4, and CPz) brain area, was used as a general index of attentional resources allocation. Regional N2–P3 amplitude was analyzed using statistical methods as described below.

2.4. Deep brain stimulation

Bilateral DBS electrodes (Medtronic 3389, Medtronic, Inc.) were implanted according to individual 3T magnetic resonance imaging (MRI) images visualizing the mamillo-thalamic tract and ANT. The initial stereotactic target of the electrodes was at 5–6 mm lateral, 12 mm superior and 0–2 mm anterior to the mid-commisural point (MCP) and further adjusted according to individual imaging data. Postoperative locations of DBS contacts were determined relative to visible borders of ANT in 3T MRI using postoperative CT – preoperative MRI fusion images. The centre between positive and negative contacts used in bipolar stimulation was defined with respect to reference lines at the posterior, anterior, medial, lateral, inferior and superior borders of ANT in each patient's left and right side (Fig. 2). During the experiment bilateral and bipolar stimulation with a frequency of 140 Hz, pulse width of 90 μs and constant current of 5 mA was used. Active contact locations were balanced between ANT and thalamic control location. When ANT was stimulated the active contact location was chosen to be the best location available for stimulating ANT, i.e. either inside or at immediate proximity of ANT and when control location was stimulated the most distant electrode from ANT was chosen as the active contact. The thalamic control locations were at the anterior or superior aspect of the dorsomedial nucleus, Fig. 2. Since bipolar stimulation was applied during the test, we calculated the mathematical centre between positive and negative contacts to estimate the actual stimulation site.

During the Executive-RT test, stimulation was turned ON or OFF alternatively

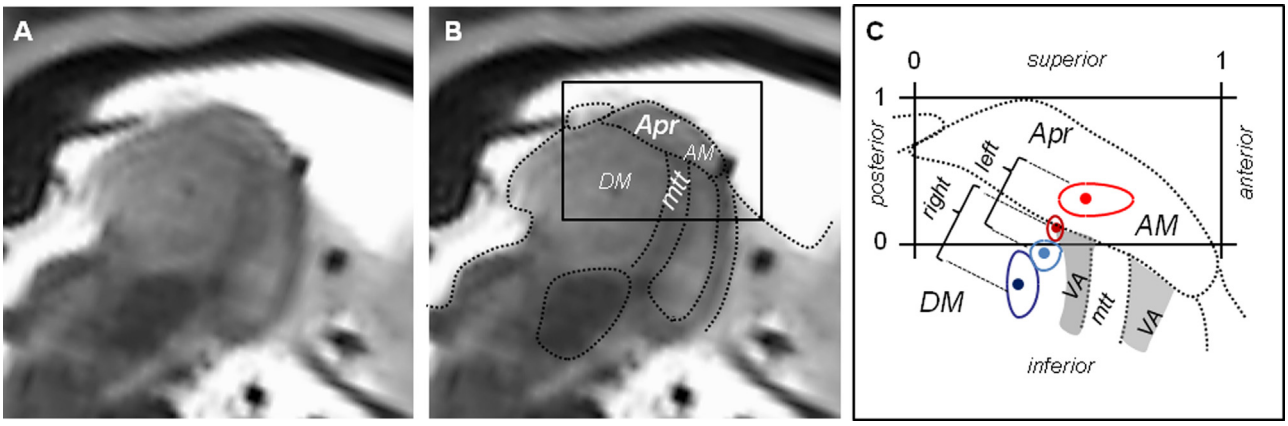

Fig. 2. The visualization of ANT nucleus and locations of stimulation sites in the thalamus. Sagittally oriented 3T MRI STIR image demonstrates the ANT nuclear complex and its subdivisions Apr and AM (A, B). The area shown as a rectangle in the panel B is illustrated in the panel C with higher magnification together with delineations of ANT borders and reference lines used in estimation of contact locations. Posterior, inferior and medial (not shown) reference lines were defined as 0 and anterior, superior and lateral (not shown) reference lines as 1. In panel C, the round shapes refer to the 25% and 75% quartile area from the median stimulation site in left side and right side. Red colour refers to stimulation site at ANT and blue colour to the stimulation at the control location. Anatomically, control location may be defined as an area bordering the three major thalamic nuclear groups (ANT, dorsomedial nucleus (DM) and ventral anterior nucleus (VA)). The area of VA is estimated according to Schaltenbrand–Wahren atlas (Schaltenbrand and Wahren, 1998) (since it is not clearly visible in sagittally oriented images) and is shown in grey in panel C. Abbreviations: Apr, anterior principal nucleus; AM, anteromedial nucleus; DM, dorsomedial nucleus; mtt, mamillo-thalamic tract; VA, ventral anterior nucleus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

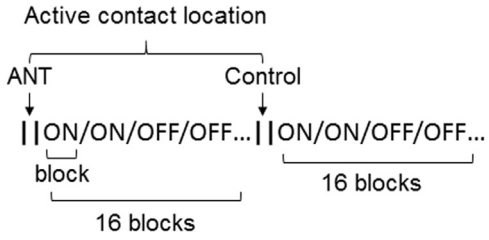

Fig. 3. Illustration of the order of blocks in experimental sessions. The order of the active contact was balanced between subjects. ANT=active contact at ANT, Control=active contact at control location, ON=Stimulation turned on, OFF=Stimulation turned off.

for 5–6 min to allow for two blocks of testing, with patients blind to the stimulator setting. During 16 blocks either ANT or thalamic control location adjacent to ANT was stimulated (512 trials each) and during 16 blocks stimulation was turned off (1024 trials). Thus, altogether 2048 trials were collected per subject. The experiment was divided into two consecutive sessions including 16 blocks each. In one session ANT was stimulated during two blocks of testing and then the stimulator was turned off for another two blocks and this was repeated four times. Identical testing sessions for stimulating the control location was carried out. The order of sessions was balanced between subjects, having three patients (patient 1, 2 and 4) with ANT firstly stimulated and the other three patients with control location as the first stimulated location, Fig. 3.

2.5. Statistical analysis

The impact of the emotional and neutral distractors to reaction times and ERPs within a Stimulation Status were analyzed using Wilcoxon signed rank test where the effect of Emotion (neutral, emotional) was compared when stimulation was ON at ANT, ON at the control location and OFF. Symmetry of differences for Wilcoxon signed rank test was ensured with Miao, Gel, and Gastwirth symmetry test. The impact of the distractors across Stimulation Statuses was compared using asymptotic K-Sample Fisher–Pitman permutation test.

Errors were analyzed using binary logistic regression. Separate models were created for the three error types, i.e. incorrect button presses, commission errors and missing responses, with each model predicting patients' probability to make a corresponding error. Outcome variable (error) was dichotomized for binary logistic regression so that for incorrect button presses outcome was either "incorrect" or "other" (correct button press or a miss), for missing button presses either "miss" (failure to respond within a given time) or "other" (any button press in a Go trial) and for commission errors either "commission error" (a failure in withholding from responding in a NoGo-trial) or "no response" (adequately withholding from responding in a NoGo trial). Subject, Stimulation Status, Emotion and Interaction between Emotion and Stimulation Status were used as predictor variables, all coded as dummy variables. In case of interaction data was stratified into sub models in order to find out specific parameters driving the interaction.

3. Results

3.1. Behavioural data

Wilcoxon signed rank test indicated that when ANT was stimulated the emotional distractors induced a statistically significant increase in subject's reaction time compared to neutral distractors ($Z=-2.2014$, $p=0.03$; Fig. 4, Table 2). There were no

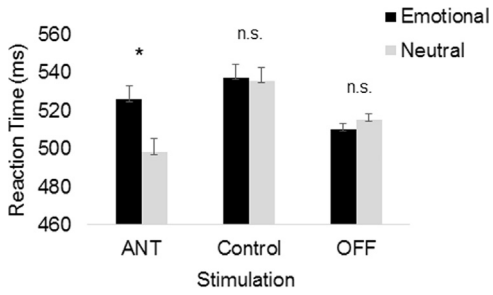

Fig. 4. Increased emotional interference due to ANT–DBS. (A) The RTs were modulated by the valence of the distractors with longer RTs in context of emotional distractors in comparison to neutral distractors when ANT was stimulated. The reaction times did not differ due to emotional valence of the distractor when DBS was OFF (B) and when the control location was stimulated (C). There were no difference in RTs between Stimulation Statuses for the same distractor. n.s.=no significance.

Table 2
Reaction times of individual patients.

Patient number	ANT		Control		OFF	
	Emotional	Neutral	Emotional	Neutral	Emotional	Neutral
1	734	719	703	684	657	665
2	387	340	413	410	367	366
4	615	590	505	503	525	537
5	460	435	639	626	542	552
10	599	557	573	583	620	617
13	359	348	393	409	351	356

Table lists reaction time in milliseconds. ANT=active contact at ANT, Control=active contact at control location, OFF=Stimulation turned off. Emotional=threat-related distractor, Neutral=non-threatening distractor

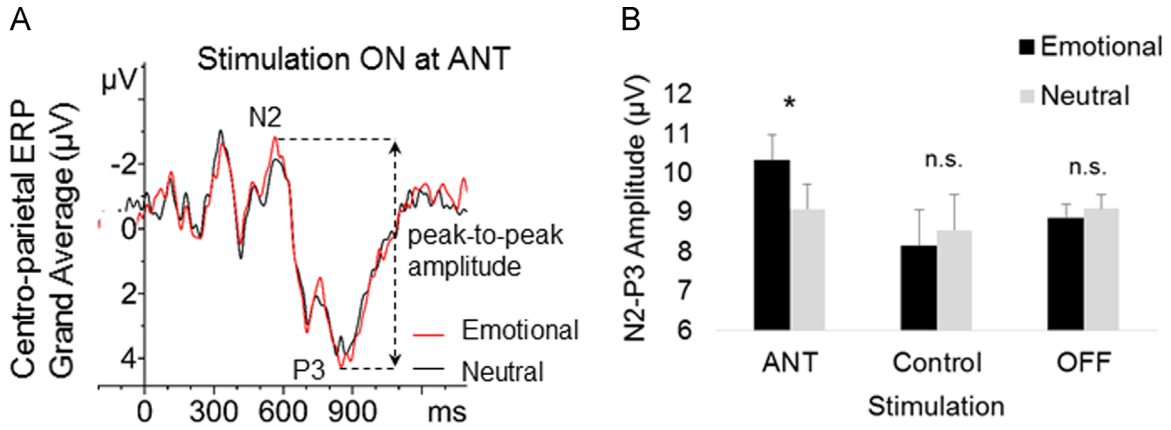

Fig. 5. Increased attention capture by emotional stimuli due to ATN–DBS. (A) Grand average ERP of the centro-parietal region demonstrating N2–P3 peak-to-peak amplitude during ANT stimulation. When ANT was stimulated, N2–P3 peak-to-peak amplitude was increased in context of emotional distractors compared to neutral distractors. (B) Stimulating the anterior thalamic nuclei increased attentional allocation to emotional distractors, as indicated by increased N2–P3 amplitude. There was no difference in N2–P3 peak-to-peak amplitude between Stimulation Statuses for the same distractor.

Table 3
Centro-parietal N2–P3 amplitudes for individual patients.

Patient number	ANT		Control		OFF	
	Emotional	Neutral	Emotional	Neutral	Emotional	Neutral
1	5.47	4.89	4.68	3.81	4.51	4.92
2	7.81	7.23	6.79	8.32	5.98	7.25
4	5.97	4.01	3.61	3.11	4.50	3.90
5	25.07	21.78	15.48	18.87	19.34	20.02
10	4.96	3.77	6.83	6.15	5.31	5.21
13	12.68	12.22	11.61	11.09	13.53	13.31

Table lists ERP amplitude in microvolts.

difference when stimulation was OFF ($Z=1.5724$, $p=0.12$§) or the control location was stimulated ($Z=-0.52414$, $p=0.60$). Symmetry test showed that reaction time differences were symmetric (ANT: test statistic=0.66, $p=0.49$; control location: −0.25, $p=0.80$; OFF: 0.93, $p=0.35$). Permutation test indicated no statistically significant difference in reaction times across Stimulation Statuses for neither of the distractors (neutral: $\chi^2=1.68$, $p=0.49$; emotional: $\chi^2=0.92$, $p=0.69$).

No statistically significant predictors were found for any error types (Table A.1 and A.2).

3.2. ERP data

To investigate potential attentional mechanism behind increased emotional interference ERPs were analyzed. The centro-parietal N2–P3 peak-to-peak amplitude (Fig. 5A) was used as an index of attentional allocation. Wilcoxon signed rank test indicated that when ANT was stimulated, the emotional distractors led to statistically significant increase in centro-parietal N2–P3 amplitude ($Z=-2.2014$, $p=0.03$; Fig. 5B, Table 3). There were no increase when stimulation was OFF ($Z=0.7338$, $p=0.4631$) or the control location was stimulated ($Z=0.10483$, $p=0.92$). Symmetry test showed that ERP amplitude differences were symmetric (ANT: test statistic=1.48, $p=0.20$; control location: −2.15, $p=0.15$; OFF: −0.42, $p=0.70$). Permutation test indicated no statistically significant difference in N2–P3 amplitude across Stimulation Statuses for neither of the distractors (neutral: $\chi^2=1.01$, $p=0.60$; emotional: $\chi^2=3.16$, $p=0.21$).

4. Discussion

This is the first study to provide behavioural and electrophysiological evidence for the role of ANT in emotion–attention interaction in humans. Disrupting and recovering ANT's normal function in humans while they performed a task requiring top-down control of emotional distraction showed that ANT–DBS has immediate effects on the human limbic circuitries critical for emotional processes. ANT–DBS increased automatic allocation of attentional resources to threat-related emotional distractors.

ANT has been thought to be involved in human executive and emotional functions mainly due to its projections to the OFC and the ACC (Child and Benarroch, 2013). Further evidence of ANT's role in affective function comes from clinical evidence of patients with anterior thalamic lesion. Lesions to this area reportedly lead to apathy and aggressiveness (Lanna et al., 2012). Depression related side effects reported by epileptic patients treated with ANT–DBS further point to a possible role of ANT and its circuits in affective functions (Fisher et al., 2010; Möddel et al., 2012). ANT's cortical connections, i.e. OFC and ACC, are also involved in emotion and executive functions (Bush et al., 2000).

We have provided unique ERP evidence from humans that ANT–DBS increases attention allocation to threat-related distractors. However, the current study does not address what aspect of the circuitry other than ANT are involved and how. We can only speculate on the role of other brain regions connected to ANT such as the OFC and ACC that may be involved. The OFC plays an important role in modulating brain's responses to affective stimuli by filtering task-irrelevant affective stimuli (Rule et al., 2002; Shimamura, 2000) as well as allocating attention to emotionally relevant stimuli (Hartikainen et al., 2012). Thus, increased attention allocation to emotional distractors due to ANT–DBS might either reflect the OFC's disrupted function in filtering threat-related distractors or enhanced function in allocating attention to them. On the other hand, the dACC is thought to integrate information from other brain regions for determining and regulating the allocation of appropriate amount of executive control resources of the lateral prefrontal cortex (Shenhav et al., 2013). Thus, with ANT–DBS disrupting input from ANT to ACC inadequate allocation of control resources of the lateral prefrontal cortex would result in inefficient top-down control of emotional distractors.

Deficient prefrontal top-down control is thought to be a potential cause for greater attention allocation to negative emotional information in mild traumatic brain injury with susceptibility to depression (Mäki-Marttunen et al., 2015). Increased attention allocation to negative information is also observed in depression (Leppänen, 2006; Matthews and Wells, 2000). Similar to depression, greater attention capture by negative emotional stimuli was seen during ANT–DBS as evidenced by prolonged reaction times

Table A.1
Average error rates under different Stimulation Statuses and with different emotional distractors.

Stimulation status	Incorrect (%)		Miss (%)		Commission errors (%)	
	Emotional	Neutral	Emotional	Neutral	Emotional	Neutral
ON at ANT	5.1	5.0	1.4	1.2	3.5	3.3
ON at Control	6.8	6.4	2.0	1.7	2.9	2.9
OFF	4.8	4.4	1.6	1.6	2.7	3.3

Table A.2
Summary of statistical results for all error types.

Predictors	Incorrect	Miss	Commission errors
Intercept	0.07 (0.05–0.10)	0.01 (0.00–0.02)	0.00 (0.00–0.01)
Stimulation status:			
ON at control	1.38 (1.00–1.92)	1.50 (0.83–2.69)	0.78 (0.51–1.20)
OFF	0.90 (0.66–1.21)	1.19 (0.70–2.03)	0.72 (0.49–1.05)
Emotion:			
Neutral	0.97 (0.68–1.38)	0.85 (0.44–1.63)	0.93 (0.61–1.43)
Emotion × stimulation status:			
ON at control × emotion flower	0.95 (0.59–1.51)	0.97 (0.41–2.29)	1.07 (0.58–1.98)
OFF × emotion flower	0.94 (0.61–1.45)	1.00 (0.46–2.20)	1.37 (0.81–2.32)

Results of logistic regression analysis of all error types with Odds Ratio followed by 95% Confidence Interval in parenthesis.

and increased centro-parietal N2–P3 amplitude in the context of emotional distractors. Thus, we contend that greater attention capture by negative emotional stimuli due to deficient frontal control might be the neural mechanism underlying subjective depression related symptoms in ANT–DBS (Fisher et al., 2010; Möddel et al., 2012).

The increase in centro-parietal N2–P3 peak-to-peak amplitude in response to emotional distractors, along with emotional interference of RTs, provide possible biomarkers for DBS effects on limbic circuitry and altered emotion–attention interaction possibly linked with affective symptoms. N2–P3 peak-to-peak amplitude measure cancelling out any overlapping positive or negative slow waves or shifts makes it a more robust measure than single N2 or P3 peak measurement, especially when used in patient populations such as epilepsy patients with high inter-individual variability in ERP waveforms. Such biomarkers of DBS effects on affective functions have clinical significance especially when DBS is used for treating depression (Mayberg et al., 2005) as well as when trying to minimize affective symptoms reported as side effects of ANT–DBS (Fisher et al., 2010; Möddel et al., 2012).

Any potential biomarkers for guiding the selection of DBS parameters towards best treatment effect with minimal side effects would be of utmost clinical importance given the vast number of possible parameter combinations and complexity of responses that make parameter optimization challenging. In current clinical practice there are no efficient tools for assessing the immediate effects of chosen stimulation parameters on cognition and emotion that would help guide parameter selection towards either wanted affective and behavioural effects or minimal side effects in various clinical populations amenable to DBS. Concomitantly, there are no objective measures for assessing alterations in emotional functions. Applying a computer-based reaction time test engaging multiple executive functions while tapping into emotion–attention interaction and by comparing ERPs during different stimulator settings as was done in the current study shows initial promise as an approach that might allow one to minimize neuropsychiatric side effects in DBS parameter selection.

While the current study provides novel evidence of ANT's role in human emotion–attention interaction, there are limitations. The patient population in this study was small and heterogeneous and several factors other than DBS could affect emotion–attention interaction and ERPs in these patients, including epileptic activity, underlying epilepsy aetiology and patient medications. These factors were controlled for in the current study by applying a within-subject design. Further, the current finding might not be generalizable to clinical situations where the stimulation parameters are somewhat different (Fisher et al., 2010). Whether ANT–DBS is impairing the normal top-down control of emotion toward increased attention allocation to threat or enhancing possibly blunted bottom-up influence of emotional stimuli toward normalized emotion–attention interaction is not clear from this study. Future studies with more patients are required to shed more light on these issues.

In addition to ANT, the thalamus includes other structures implicated in emotional pathways and emotion–attention interaction, e.g. mammillothalamic tract (MacLean, 1949; Papez, 1937) and pulvinar (Arend et al., 2015; Ward et al., 2007). It is possible that these structures also contribute to the effects observed in this study. In order to distinguish the general effects of brain stimulation from the region specific effects of ANT stimulation a thalamic control location in the vicinity of ANT a few millimetres away toward the medial thalamus was also stimulated. Unlike ANT stimulation, stimulating the control location did not result in increased attention allocation to threat-related distractors. Also, since the thalamus is a physically a large structure, approximately 3.5 cm in length, 2–2.5 cm in transverse and approximately 6.5–7 cc in volume (Sen et al., 2005; Spinks et al., 2002), and the DBS Volume of Tissue Affected (VTA) relatively small (Montgomery, 2010), in our case few millimetres from the stimulation focus with 5mA bipolar stimulation, we can assume that the effect of electric stimulation is local to ANT. Taken together, the small VTA and no stimulation effect in the thalamic control location support the specific role of ANT and its networks in emotion–attention interaction.

In conclusion, this study elucidates the important role of ANT in emotion–attention interaction. By stimulating ANT, increased attentional resources were allocated to emotional distractors, possibly indicating inefficient top-down control. Altered emotion–attention interaction as a function of ANT–DBS points towards ANT as an intersection for attention and emotion circuitries. In addition, ANT–DBS increasing attentional allocation to threat highlights the need to consider affective side-effects in addition to the

therapeutic effect when optimizing DBS stimulator settings.

Conflict of interest

The authors declare no conflict of interest.

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Appendices

see Table A.1 and A.2

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