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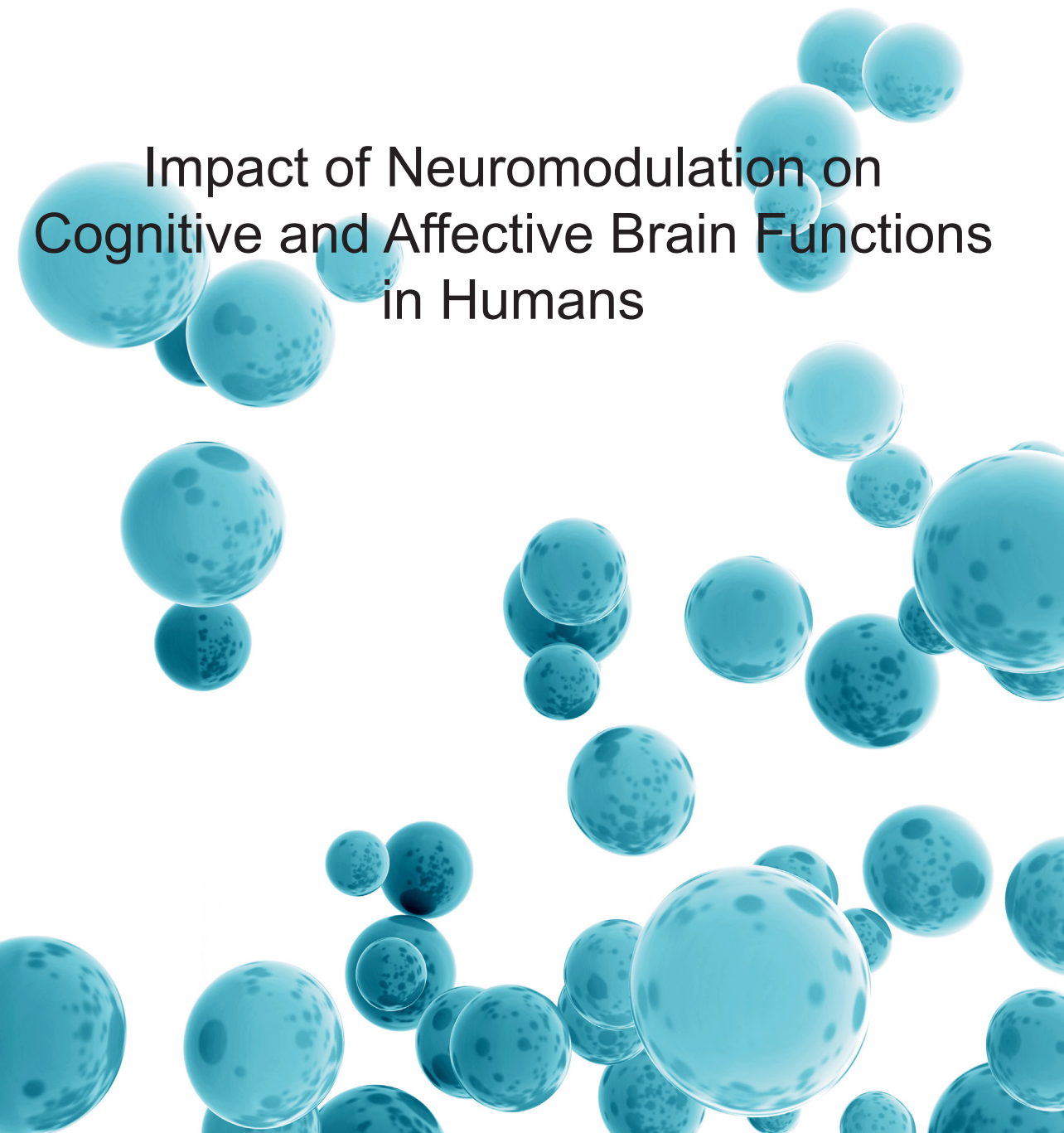
LIHUA SUN

Impact of Neuromodulation on Cognitive and Affective Brain Functions in Humans



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ACADEMIC DISSERTATION
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ACADEMIC DISSERTATION
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Preface

Neuromodulation refers to the approach of using physical intervention to interfere with the nervous system and modify its functioning with the purpose of bringing benefits. It aims to restore the function of disrupted neural circuits and to relieve neurological and psychiatric symptoms. For instance, high frequency electrical stimulation at the anterior thalamic nuclei (ANT) is thought to reduce ANT's function to disrupt epileptic propagation. Despite the rapid development of neuromodulation techniques mechanism of action remains unknown. Given their potential neurologic and psychiatric benefit an understanding of the modulated neural circuits is critical.

Neuromodulation treatments, such as deep brain stimulation at the ANT (ANT-DBS) and vagus nerve stimulation (VNS), are used in the treatment of refractory epilepsy. In addition to reducing seizure intensity, affective and cognitive circuits may also be influenced, resulting in alteration in cognitive and affective functions. For example, VNS is shown to reduce seizure frequency and is suggested to improve mood and affect cognition. Similarly, ANT-DBS has been reported to reduce seizure frequency, but subjective memory problems and depression-related symptoms have been reported. General concern of life quality and the uncertainty surrounding cognitive and affective alterations might restrain the use of these neuromodulation techniques. Because of these concerns a deeper understanding of how neuromodulation affects human cognition and emotion is critical, not only to understand the underlying neural circuits but also to benefit clinical treatments.

This thesis aims to elucidate the effect of three neuromodulation techniques on human cognition and emotion. The study bears both neuroscientific significance at better understanding the neural circuits underlying cognitive and affective behavior and clinical significance in identifying potential biomarkers to help optimize treatment. This work was conducted in the Behavioral Neurology Research Unit of Tampere University Hospital and is supported by grants awarded to Dr. Kaisa M. Hartikainen, M. D., Ph. D. from the Academy of Finland and the Competitive Research Fund of Pirkanmaa Hospital District.

I am indebted to my Ph. D. supervisor Dr. Kaisa M. Hartikainen for leading me into this research field. She has been so encouraging and took me as a Ph. D. student despite my lack of knowledge in both psychology and neurology which is crucial for doing research in the field of behavioral neurology. She has been so patient in guiding me in every detail of the work, including scientific thinking, experimental design and

writing articles. Also, she shared her experience of how to build an academic career, which will be a benefit throughout my life.

All this work would have never been possible without the support of the lab members of the Behavioral Neurology Research Unit of Tampere University Hospital: Jari Peräkylä, Maarja Brause, Venla Kuusinen, Markus Polvivaara, Katri Holm, Anselmi Kovalainen, Rodolpho Ribeiro and Thales-Souza Campos-Rodrigues. I especially wish to thank Jari Peräkylä for his help in statistics, scientific discussions and co-authoring most of my publications. I thank Maarja Brause for initially teaching me how to conduct EEG recordings and basics for working in the lab. I thank Markus Polvivaara and Katri Holm for building some of the ground work and making it easy for me to continue. I also thank Rodolpho Ribeiro, Thales-Souza Campos-Rodrigues and Anselmi Kovalainen for the help in studying the affective effects of extraocular light. I thank Maarja Brause, Venla Kuusinen and Karti Holm for teaching me Finnish language and Finnish Culture. Finally, I thank all of them for making such an enjoyable working environment.

I am grateful for my other two supervisors: Dr. Jukka Peltola and Professor Keith H. Ogawa. Dr. Jukka Peltola shared his expertise in clinical epileptology and recruited patients, provided clinical information and helped with experimental design. Professor Ogawa's expertise has been helpful in guiding me in the field of cognitive neuroscience and psychology. His help has been also invaluable in the scientific writing process. I also thank my Follow-up group, including Dr. Kai Lehtimäki, Dr. Ville Jäntti and Dr. Jukka Leppänen. I especially thank Dr. Kai Lehtimäki for his expertise in neuroanatomy and opening a new window for me into modern neurosurgery as well as his help in recruiting patients, providing surgical images and helping with the data collection.

I also wish to thank the other co-authors of the publications whose contributions made these publications possible: Professor Juha Öhman, Professor Pekka Karhunen, Dr. Joonas Haapasalo, Timo Mönönen, Kirsi Väyrynen, and Heini Huhtala.

I thank Professor Juhani Väinö Partanen from Helsinki University Hospital and Professor Notger Müller from Otto-von-Guericke University for revising my thesis.

Finally, I especially thank my wife Cai Li for completing my happiness. She has been a wonderful supporter for all works. I also thank my whole family in China for their support in all aspects of my life.

Lihua Sun
Summer, 2016

Contents

Abstract

Background: Neuromodulation techniques have been proposed to restore disrupted neural circuits and are used to treat neurological and psychiatric disorders. The techniques used in the current thesis include deep brain stimulation (DBS), vagus nerve stimulation (VNS) and non-invasive extraocular photomodulation. Many neuromodulation approaches affect cognitive and limbic circuitries, and thus their influence extend to affective and cognitive effects. In addition to their use in medical treatment, they provide unique opportunities to study brain networks underlying human cognition and emotion.

Aims: Since cognitive and emotional health is critical for life quality, optimal medical treatment should alleviate symptoms of the disease while minimizing adverse cognitive and emotional effects. Therefore, elucidating the effects of neuromodulation on human cognition and emotion are neuroscientifically valuable and clinically essential. This thesis aims to measure the effects of neuromodulation on human executive functions and to investigate the underlying cognitive and affective circuits. Furthermore, the study aims to investigate the role of a deep brain structure, i.e., the anterior thalamic nuclei (ANT), in emotion-attention interaction and to provide potential biomarkers to help optimize the medical treatment.

Methods: The computer-based Executive-RT test has been shown to be a sensitive tool to detect subtle changes in human cognitive and affective functions. It is a Go/NoGo visual attention task engaging several executive functions, including working memory, response inhibition and emotional control. Different groups of subjects participated in the study, including patients with ANT-DBS and VNS treatment for epilepsy, and young healthy individuals. Subjects' performance was evaluated when neuromodulation was on and when it was off, revealing the immediate effects of neuromodulation. Further, EEG was recorded to measure brain electrophysiological changes and to investigate brain mechanisms of the observed behavioral changes.

Results: Patients with ANT-DBS treatment for epilepsy performed the Executive-RT test while DBS was either on or off. When DBS was on at ANT, patients had increased reaction times (RTs) in the presence of threat-related distractors compared to the emotionally neutral control distractors. In contrast, the

valence of the distractors had no effect on RTs when DBS was off. The increase in RTs suggest increased impact of threat-related distractors on behavior due to ANT-DBS. Along with an increase in RTs there was an increase in centro-parietal N2-P3 amplitude indicating increased attention allocation to threat due to ANT-DBS.

Twenty patients undergoing VNS for epilepsy performed the Executive-RT test with the stimulation cycling alternatively on and off. VNS improved working memory performance and increased parieto-occipital N1 amplitude suggesting enhanced visual attention. Also, VNS slowed RTs and increased right hemispheric activity in the presence of threat-related distractors, as indicated by increased frontal alpha asymmetry, suggesting increased vigilance to threat.

Eighteen healthy subjects performed the Executive-RT test while extraocular light was delivered via the ear canals and when it was not. The extraocular light did not affect the behavioral performance. Nevertheless, the ear-canal-delivered extraocular light diminished the modulatory effects of threat-related distractors on parietal P3 amplitude. Specifically, when the light headset was off threat-related distractors led to decreased P3 amplitude compared to neutral distractors. This phenomenon disappeared when the ear headset was on. Also, we showed that the extraocular light was able to penetrate the skull of a human cadaver via the ear canals.

Conclusions: Behavioral testing and EEG recording combined with periodic administration of neuromodulation is a sensitive and potentially viable method to study the immediate effects of neuromodulation on human cognition and emotion. Using ANT-DBS, we illustrated the important role of ANT in human emotion-attention interaction with direct behavioral and electrophysiological evidence from humans. Previously, ANT's role in human emotion has been mainly inferred from its connection with other limbic structures. Increased attention allocation to threat, a hallmark of anxiety and depression (along with the previously reported subjective increase of depression related symptoms), calls for careful consideration of possible affective side effects of DBS in the treatment of epilepsy. The study using VNS showed the immediate cognitive benefits in patients with epilepsy. In patients with epilepsy cognition may be compromised due to several factors, including epilepsy and antiepileptic drugs. Demonstrating that VNS with clinically relevant stimulation parameters has significant benefit on cognition bears clinical significance. VNS also has an immediate impact on the brain's emotional responses to threat-related stimuli. In addition, extraocular photomodulation affecting the brain's emotional control indicates that the human brain reacts to extraocular light, calling for further investigation on the effects of extraocular light on human brain physiology.

These studies bear clinical significance by providing potential behavioral and electrophysiological biomarkers for the cognitive and affective effects of neuromodulation treatment. The change of RTs in the Executive-RT test might be a potential behavioral marker for affective modulation. Both ANT-DBS and VNS increased reactivity to threat as indicated by the changes of RTs. Meanwhile, the centro-parietal N2-P3 peak-to-peak amplitude and the frontal alpha asymmetry might be potential biomarkers for the altered in emotion-attention interaction due to neuromodulation. Immediate cognitive benefits of VNS are relevant in today's clinical practice in treating patients with epilepsy. Furthermore, the current results call for future studies for the potential usefulness of VNS as a clinical intervention in cognitive impairment and attentional deficits.

Tiivistelmä

Tausta: Erilaisten neuromodulaatiotekniikoiden on esitetty korjaavan hermoratojen häiriöitä ja näitä hoitomuotoja käytetäänkin neurologisten ja psykiatristen sairauksien hoidossa. Neuromodulaatiotekniikoita ovat mm. syväaivostimulaatio (Deep Brain Stimulation, DBS) ja vagushermon stimulaatio (Vagus Nerve Stimulation, VNS) sekä ei-invasiivisena keinona silmänulkoinen valostimulaatio. Monet neuromodulaatiomenetelmät vaikuttavat kognitiivisiin ja limbisiin radastoihin, joten modulaatio vaikuttaa näin ollen myös kognitiivisiin ja tunteisiin liittyviin aivotoimintoihin. Hoitotarkoituksensa lisäksi neuromodulaatiotekniikat antavat täten mahdollisuuden tutkia ihmisen kognition ja tunteiden taustalla olevia hermoverkostoja.

Tavoitteet: Koska ihmisen kognitiivinen toimintakyky ja tunnesäätely ovat tärkeitä elämänlaadun kannalta, lääketieteellisen hoidon tulisi helpottaa sairauden oireita siten, että se ei samalla aiheuttaisi sivuvaikutuksia tunne- ja tiedonkäsittelytoimintoihin tai jos sivuvaikutukset ovat väistämättömiä ne minimoitaisiin. Tästä syystä se, miten neuromodulaatio vaikuttaa kognitiiviseen toimintakykyyn ja tunnesäätelyyn on sekä tieteellisessä että kliinisessä mielessä merkittävää. Tämän väitöskirjan tarkoituksena on selvittää neuromodulaation vaikutuksia ihmisen toiminnanohjaukseen ja tunnetoimintoihin ja tutkia näiden toimintojen taustalla olevia hermoverkostoja. Lisäksi tutkimuksen tavoitteena on selvittää talamuksen etumaisten tumakkeiden (Anterior Nuclei of Thalamus, ANT) roolia tunteiden ja tarkkaavaisuuden säätelyssä sekä löytää biomarkkereita, joiden avulla neuromodulaatiohoitoja olisi mahdollista optimoida.

Menetelmät: Tietokonepohjaisen ”Executive-RT” testin on osoitettu olevan herkkä havaitsemaan pieniä muutoksia ihmisen kognitiivisissa ja affektiivisissa toiminnoissa. Testi on Go/NoGo -tyyppinen tarkkaavaisuustehtävä joka kuormittaa laajalti toiminnanohjaustoimintoja mukaan lukien työmuisti, vasteenestotoiminnot ja tunnekontrolli. Tutkimuksissa on käytetty kahta potilasryhmää – epilepsiasta kärsiviä potilaita joilla on hoitona joko ANT-DBS tai VNS – sekä nuoria, terveitä koehenkilöitä. Koehenkilöiden pärjäämistä testissä arvioitiin neuromodulaation ollessa päällä ja pois päältä, jolloin voidaan arvioida modulaation välittömiä vaikutuksia. Lisäksi rekisteröitiin aivosähkökäyrää, jonka perusteella tutkittiin

mahdollisia tarkkaavaisuuteen liittyviä aivomekanismeja havaittujen käyttäytymismuutosten taustalla.

Tulokset: Potilaat, joilla on DBS-hoito vaikean epilepsian vuoksi tekivät ”Executive-RT” testiä stimulaation ollessa vuoron perään päällä tai pois päältä. Kun ANT:ta stimuloitiin, hidastuivat koehenkilöiden reaktioajat vasteena uhkaavaan häiriöärsykkeeseen (hämähäkki) tunnesisällöltään neutraaliin kontrolliärykkeeseen (kukka) verrattuna. Lisäksi centro-parietaalinen N2-P3 herätevasteamplitudi kasvoi osoittaen lisääntynyttä tarkkaavuusresurssien suuntaamista uhkaavaan häiriöärsykkeeseen.

Kaksikymmentä potilasta, joilla on epilepsian hoitona VNS laitteisto, suorittivat vastaavan kokeen. VNS-stimulaation havaittiin parantavan työmuistia ja lisäksi parieto-occipitaalinen N1 herätevasteamplitudi kasvoi sopien lisääntyneeseen visuaalisen tarkkaavaisuuteen. VNS:n pälläolo hidasti myös reaktioaikoja ja lisäsi oikean aivopuoliskon aktiivisuutta uhkaavaan ärsykkeeseen EEG:n frontaalisen alfa-taajuuden asymmetrialla mitattuna. Oikean aivopuoliskon aktiivisuuden lisääntyminen sopii lisääntyneeseen valppauteen negatiiviseen uhkaärsykkeeseen liittyen.

Kahdeksantoista tervettä koehenkilöä teki Executive-RT kokeen samalla, kun he saivat silmänulkoista valostimulaatiota korvakäytävään asetetusta valonlähteestä. Korvavalo oli vuoronperään päällä ja pois päältä. Valolla ei havaittu vaikutusta koehenkilöiden kognitiiviseen suorituskykyyn. Korvavalolla oli kuitenkin vaikutus parietaaliseen P3-amplitudiin uhkaaviin häiriöärsykkeisiin liittyen. Kun valo oli kytkettynä pois päältä, uhkaava ärsyke lisäsi parietaalista P3-amplitudia, mutta tämän ärsykkeen vaikutus hävisi korvavalon ollessa päällä. Osoitimme lisäksi vainajalla, että korvakäytävään asetettu valo läpäisee kallonpohjan.

Päätelmät: Käyttäytymistesti yhdistettynä aivojen sähköisen toiminnan rekisteröintiin ja jaksottaiseen stimulaatioon on herkkä ja mahdollisesti yleisemminkin käytettäväksi soveltuva keino neuromodulaation välittömien kognitiivisten ja affektiivisten vaikutusten arvioimiseksi. ANT-DBS:n kohdalla osoitimme ANT:n olennaisen roolin ihmisen tunteiden ja tarkkaavaisuuden välisessä vuorovaikutuksessa. Aiemmin ANT:n rooli affektiivisissa toiminnoissa on päätelty lähinnä sen yhteyksistä muihin limbisiin rakenteisiin. Tarkkaavaisuusresurssien lisääntynyt suuntaaminen uhkaavaan ärsykkeeseen on tyypillistä ahdistuneisuudelle ja masentuneisuudelle. Yksi ANT-DBS:n raportoiduista sivuvaikutuksista on masennus, joten affektiivisten sivuvaikutusten arviointi ANT-DBS -hoidossa on olennaista. VNS:llä oli välitön suotuisa vaikutus epilepsiaa sairastavien potilaiden kognitoon, erityisesti työmusitiin ja tarkkaavuuteen. Epilepsia altistaa kognition

häiriöille monilla eri mekanismeilla. Siten on kliinisestikin merkittävää, että VNS, jota käytetään vaikean epilepsian hoitoon kohentaa kognitiivisa toimintoja. Korvan kautta annetun valon vaikutus tunnepitoisten ärsykkeiden käsittelyyn osoittaa ihmisen aivojen reagoivan myös muualta, kuin silmän kautta tulevaan valoon. Tämä löydös antaa aihetta lisätutkimuksille valon vaikutuksesta ihmisen hermostoon ja aivotoimintaan.

Väitöskirjan tutkimuksilla on potentiaalista kliinistä merkitystä mahdollisten käyttäytymiseen tai aivosähkötoimintaan liittyvien biomarkkereiden löytämisen kautta. Biomarkkerit liittyvät eri neuromodulaatiomuotojen kognitiivisiin- ja tunnevaikutuksiin. Sekä ANT-DBS että VNS vaikuttivat uhkaavan ärsykkeen käsittelyyn ja reaktioaikojen muutokset voivat toimia tämän vaikutuksen biomarkkerina. Centro-parietaalinen N2-P3 amplitudi ja frontaalinen alfa-asymmetria ovat lupaavia biomarkkereita neuromodulaation aiheuttaman tunteiden ja tarkkaavaisuuden välisen säätelyn muutosten osalta. VNS-stimulaation välittömät positiiviset vaikutukset kognitioon ovat merkittäviä epilepsiapotilaiden hoidon kannalta jo nykypäivänä ja lisäksi kannustavat tutkimaan tulevaisuuden mahdollisuuksia laajentaa VNS-hoitoa kognitiivisten häiriöiden ja tarkkaavaisuushäiriöiden hoidossa.

List of Original Publications

The thesis is written on the basis of four original publications. Publications are listed below and referred to in the text by their Roman numerals:

I. Hartikainen Kaisa M., Sun Lihua, Polvivaara Markus, Brause Marja, Lehtimäki Kai, Haapasalo Joonas, Möttönen Timo, Väyrynen Kirsi, Ogawa Keith H., Öhman Juha, Peltola Jukka. (2014) Immediate effects of deep brain stimulation of anterior thalamic nuclei on executive functions and emotion-attention interaction in humans. Journal of Clinical and Experimental Neuropsychology 36 (5), 540-550.

II. Sun Lihua, Peräkylä Jari, Polvivaara Markus, Öhman Juha, Peltola Jukka, Lehtimäki Kai, Huhtala Heini; Hartikainen Kaisa M. (2015) Human anterior thalamic nuclei are involved in emotion-attention interaction. Neuropsychologia 78: 88-94

III. Sun Lihua, Peräkylä Jari, Holm Katri, Haapasalo Joonas, Lehtimäki Kai, Ogawa Keith H., Jukka Peltola, Hartikainen Kaisa M. Vagus nerve stimulation improves working memory performance. (submitted)

IV. Sun Lihua, Peräkylä Jari, Kovalainen Anselmi, Ogawa Keith H., Karhunen Pekka J., Hartikainen Kaisa M. (2016) Human Brain Reacts to Transcranial Extraocular Light. PLoS ONE 11 (2).

Author's Contribution

All the listed publications are virtually a group effort. My contribution for these publications involves experimental design, recordings of behavioral and EEG data, data analysis and writing. I have taken principal responsibility for data analysis within all four publications and shared responsibility for writing in publication II, III and IV.

Aims of the Study

This thesis has the following aims:

a. To uncover the immediate effects of ANT-DBS on human cognition and emotion.
b. To investigate the role of deep brain structures, i.e., ANT and its neural circuits, in emotion-attention interaction and executive functions.
c. To uncover the immediate effects of VNS on human emotion, attention and executive functions, especially working memory.
d. To investigate whether the human brain is sensitive to extraocular light.
e. To identify behavioral and electrophysiological biomarkers of the cognitive and affective effects of neuromodulation.

Abbreviations

ACC	anterior cingulate cortex
AEDs	antiepileptic drugs
ANT	anterior nuclei of thalamus
DBS	deep brain stimulation
EEG	electroencephalogram
ERP	event-related potential
Executive-RT test	executive reaction tme test
Hz	hertz
IAPS	international affective picture system
IPG	implantable pulse generator
mA	milliamperes
mm	millimeters
ms	milliseconds
MTBI	mild traumatic brain injury
NE	norepinephrine
OA	outside ANT
OFC	orbitofrontal cortex
PFC	prefrontal cortex
RT	reaction time
SAD	seasonal affective disorder
TLE	temporal lobe epilepsy
VNS	vagus nerve stimulation
μV	microvolts

1 Introduction

Neuromodulation refers to the approach of using some type of intervention that interferes with the nervous system and modifies its functioning with the purpose of bringing benefits (Arle, 2011). The types of intervention are multiple, involving pharmacological, electrical, magnetic, or light-mediated techniques. Depending on the disorder, the neural targets subjected to neuromodulation also vary, including circuits of the brain, spinal cord and peripheral nerves. For example, in deep brain stimulation (DBS) an electrical current is used to modulate specific neural circuits of the brain. Given that large amount of patients with neurological and psychiatric disorders (e.g., refractory epilepsy, Alzheimer's disease, treatment resistant major depression, etc.) remain disabled even after the best available medical treatment, novel and efficient neuromodulation approaches are needed.

Brain targets subjected to neuromodulation, such as DBS, are often associated with the limbic and associative circuitries (Hartikainen, 2015). Modifying key nodes of limbic circuits may bring cognitive and affective effects. For instance, DBS at the ANT, while efficient in reducing seizures, may result in adverse effects, including subjectively reported memory decline and depressive symptoms possibly due to disrupted ANT functioning (Fisher et al., 2010; Salanova et al., 2015). ANT has critical role in emotional processing as it is a key node of the Papez circuit (Papez, 1937), and in human cognitive control function in light of its direct connection with the prefrontal cortex (Child and Benarroch, 2013). Optimal neuromodulation treatment is supposed to be efficient in reducing the targeted pathological symptoms while having minimal side effects on cognition and emotion. Therefore, elucidating these cognitive and affective effects are clinically beneficial, allowing for deeper understanding of the potential cognitive and emotional effects of neuromodulation as well as allowing to identify possible biomarkers. On the other hand, this study would expand our knowledge of the neural circuits behind human cognition and emotion, providing widespread benefits.

Traditional neuropsychological testing may not be suitable for detecting subtle immediate cognitive and affective effects due to neuromodulation. Meanwhile, studies of the long-term effects are often confounded with several uncontrollable factors, including medication, changes in social dynamics and natural course of the

illness. The Executive-RT test has been shown sensitive to alteration in affective and cognitive functions such as increased attention allocation to threat due to mild traumatic brain injury (Hartikainen et al., 2010b; Mäki-Marttunen et al., 2015) and improved cognitive functions after aortic valve replacement surgery (Liimatainen et al., 2016). It is a computer-based Go/NoGo visual attention task engaging several human executive functions, including working memory, response inhibition and emotional control. The Executive-RT test can be conducted when neuromodulation is applied and when it is paused. Alteration of performance levels, as reflected in both RTs and error rates between situations when neuromodulation is administrated and when it is not, allows one to uncover the immediate and direct effects of neuromodulation.

In addition to behavioral performance, concomitant recording of electroencephalogram (EEG) provides real-time online information of the brain electrophysiology with high temporal resolution. Event-related potentials (ERPs), yielded by averaging EEG segments which are time-locked to stimuli, are directly linked to sensory, motor, affective, and cognitive processes (Luck., 2005). Particularly, ERPs allow one to uncover the attentional mechanism behind the behavioral performance (Luck et al., 2000). At the same time, ERPs are capable of demonstrating the brain's physiological alterations that are invisible in behavioral outcomes (Luck., 2005; Boly et al., 2011; Kouider et al., 2013). This makes ERPs not only an associated investigation of behavioral consequences, but also an independent tool by which to study the physiological effects of neuromodulation. Therefore, ERPs are suitable tools to study brain functioning under different neuromodulation conditions, i.e., when neural intervention is applied versus when it is paused.

In this thesis work, we studied three neuromodulation techniques by investigating their immediate effects on human cognition and emotion. These techniques include DBS, vagus nerve stimulation (VNS) and extraocular photomodulation.

2 Literature Review

2.1 Neuromodulation Techniques

Neuromodulation techniques have been used to restore disrupted neural circuits and to relieve neurologic and psychiatric symptoms. These techniques can be either electrical, magnetic or light-mediated. Neuromodulation treatments such as DBS and VNS have both local and distant modulatory effects often affecting the brain limbic circuitry leading to altered cognition and emotion. For instance, DBS at ANT has been associated with subjectively reported depression and memory related symptoms (Fisher et al., 2010). DBS for treating Parkinson's disease is found to cause severe depression when a site two mm below the targeted subthalamic nuclei is stimulated (Bejjani et al., 1999). On the other hand, chronic VNS used for treating refractory epilepsy was initially reported to improve the mood of these patients (Elger et al., 2000) and used later for treating depression (Rush et al., 2000; Marangell et al., 2002). In this thesis, we studied the effects of three neuromodulation techniques and their effects on human cognition and emotion. The current knowledge of these techniques and their cognitive and affective effects are reviewed below.

2.1.1 Deep Brain Stimulation

ANT-DBS (Fig. 1) has been approved in Europe for the treatment of refractory epilepsy since 2010. When patients with epilepsy are pharmacoresistant and not eligible for resective surgery, DBS treatment can be applied (Fisher et al., 2010; Fisher and Velasco, 2014). However, the exact mechanism of its action is still not fully understood. Possibly, high-frequency electrical stimulation disrupts the function of ANT and ceases epileptoformic activity, given ANT's critical role in epileptic propagation (Zumsteg et al., 2006; Lim et al., 2008; Nagel and Najm, 2009; Lega et al., 2010).

Meanwhile, ANT is also a key node of the limbic system and plays an important role in emotion. Patients with ANT-DBS treatment seem predisposed to depression-

related symptoms (Fisher et al., 2010; Möddel et al., 2012). However, chronic effects of ANT-DBS on emotion and cognition is a complex process with many contributing factors including medication, clinical state of epilepsy, etc. In contrast to its known efficacy in seizure control (Fisher et al., 2010; Salanova et al., 2015), there is limited knowledge on whether ANT-DBS directly affects human emotion and how this effect occurs.

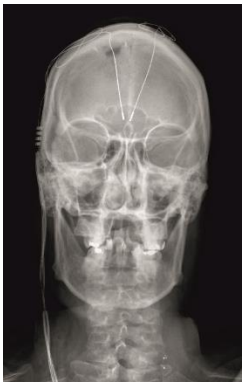

Figure 1. X-ray image of a patient with ANT-DBS treatment.

The critical location and wide projection (Xiao and Barbas, 2002a, b) of ANT have assigned it a variety of potential roles in brain functioning. One anatomical neighbor of ANT is the anterior cingulate cortex (ACC) (Child and Benarroch, 2013). The ACC has crucial role in brain functions including emotion, attention and cognitive control. This has been demonstrated in multitude of neuroimaging studies (Bush et al., 2000) and studies on patients with brain lesions (Barris and Schuman, 1953; Turken and Swick, 1999). In addition to these crucial anatomical connections, clinical evidence indicates that a single strategic lesion at ANT leading to anterograde and retrograde amnesia, apathy, inattention, and aggression also highlights its role in human cognition and emotion (Schmahmann, 2003; Nishio et al., 2011; Lanna et al., 2012).

Thus, ANT-DBS provides a unique chance to study ANT's role in general executive functions and emotion-attention interaction in humans. Understanding the potential cognitive and affective alteration due to ANT-DBS bears clinical significance.

2.1.2 Vagus Nerve Stimulation

The vagus nerve is the tenth cranial nerve and is traditionally recognized for its parasympathetic role in autonomic functions such as heart rate (Berthoud and Neuhuber, 2000). Vagus nerve stimulation (VNS) was approved in Europe for treating refractory epilepsy in 1994 and approved by the FDA in 1997 in the United States. It has also been FDA approved in 2005 for treating major depression.

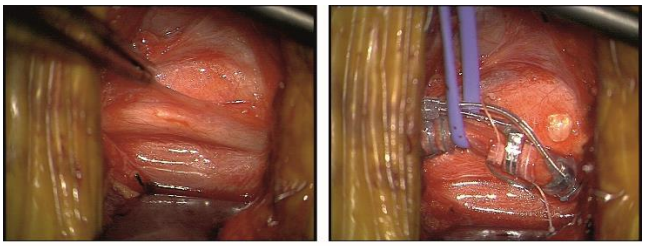

Figure 2. Implantation of the VNS electrodes (image by Kai Lehtimäki).

In clinically applied VNS treatment, the left cervical vagus nerve is usually stimulated (Fig. 2). The vagus nerve holds three types of fibers categorized on their conduction velocity (Chase et al., 1966). Two types of fibers, A and B fibers, have high conduction velocity and are easy to activate using relatively low current. The third type, C fiber, has low conduction velocity and is thought to be activated only with high current. Activation of A and B fibers is thought to synchronize brain EEG, whereas activating the C fiber desynchronizes the EEG (Chase et al., 1966).

The exact mechanism of how VNS therapy reduces seizure burden of patients with epilepsy is not fully understood (Krahl and Clark, 2012). It is proposed that VNS helps to desynchronize the thalamocortical connections and prevents seizure propagation (Korb and Helmers, 2014). Around 80% of the cervical human vagus nerve fibers are afferent, innervating the nucleus tractus solitarius which further forwards information to vast brain areas including parabrachial nucleus, locus coeruleus, and dorsal raphe nucleus (Nemeroff et al., 2006; Krahl and Clark, 2012). In contrast to the relatively well-established role of VNS in seizure control, how and whether the VNS directly modulates human cognition and emotion remains under debate (Vonck et al., 2014; Grimonprez et al., 2015a; Grimonprez et al., 2015b).

Reported chronic effects of clinically applied VNS on human cognition and emotion are controversial, with either positive or no significant changes reported

(Sackeim et al., 2001; McGlone et al., 2008). Long-term effects of VNS are confounded with the time course of clinical treatment. Meanwhile, reported benefits of immediate VNS are restricted to very specific situations, e.g. improved verbal memory only when low-intensity current was delivered (current below 1 mA) (Clark et al., 1999) and enhanced memory consolidation only when stimulation was delivered during the memory consolidation phase (Clark et al., 1995). Although the finding of Clark et al (Clark et al., 1999) led to the experimental trial of VNS in treating Alzheimer's disease (Sjogren et al., 2002), controversial results with some reporting cognitive improvement while the others not (Sjogren et al., 2002; Merrill et al., 2006) have not provided objective validation of its usefulness in intervening the cognitive decline.

Behavioral and electrophysiological changes when VNS is on compared to when it is off might provide valuable information of the direct and immediate effects of VNS on human cognition and emotion. Elucidating these immediate effects of VNS on human executive functions has significant clinical impact.

2.1.3 Extraocular Photomodulation

Bright Light Ear Headset (NPT1100, Valkee Oy, Oulu, Finland) is a commercially available product in the Finnish market. The idea behind this product is that exposing the brain to light via the ear canals might energize the body (Starck et al., 2012; Tulppo et al., 2014), Fig. 3. One of the key purposes of this product is to deal with the seasonal affective disorder (SAD). However, research supporting its usefulness in treating SAD is lacking.

SAD is characterized by symptoms including hypersomnia, increased appetite, lack of interest in social activities and impaired concentration (Rosenthal et al., 1984). SAD is often associated with the reduced amount of daylight during late fall, with remission occurring during spring as daylight hours lengthen. The symptoms of SAD possibly derive from light deficiency. Dark winter days are common in areas of the northern latitude and lengthened hours of darkness modulate circadian rhythms and hormone secretion (Dahl et al., 1993). Light therapy is usually recommended as the first line of treatment and its therapeutic effect is thought to be mediated via the eyes (Pail et al., 2011). Whether light delivery via the ear canals has similar effects is not known. It is not even known whether the human brain can react to this light or not.

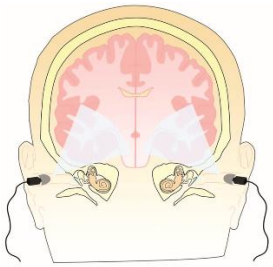

Figure 3. Illustration of the extraocular photomodulation (Sun et al., 2016).

It has been shown that light influences the behavior of birds not only through the traditional lateral geniculate striate pathway but also via deep brain photoreceptors (Foster et al., 1985; Nakane et al., 2010). These deep brain photoreceptors, such as Opsin 5, respond to low level transcranial extraocular light, especially blue light, and modulate behaviors such as seasonal breeding (Nakane et al., 2010). Light can penetrate the skull of mammals and the penetrated ambient light is able to enhance potassium-induced release of γ-aminobutyric acid in cortical neurons of rats (Wade et al., 1988). However, whether the mammalian brain possesses similar extraocular photosensitivity as in birds is unknown (Foster et al., 1994; Blackshaw and Snyder, 1999; Bromundt et al., 2014). It is even unknown whether visible light is able to penetrate the relatively thick human skull.

2.2 Human Executive Functions

Executive functions refer to cognitive and affective control processes in goal-directed behavior (Cicerone et al., 2000). Executive functions are needed for holding current goals in mind, choosing between multiple choices of actions and thoughts, and overriding automatic or habitual responses in order to reach the final goal. These functions may include variable components depending on the specific field of study (Purdy, 2011). Typically, human executive functions can be divided into cognitive processes including working memory, rule shifting, planning, initiation, response inhibition and self-monitoring (Stuss and Benson, 1986; Rabin et al., 2006).

Executive functions require integrated function of many different parts of the brain, particularly the prefrontal cortex (Alvarez and Emory, 2006). The prefrontal cortex is located at the frontal brain region anterior to the premotor cortex and supplementary motor area (Zelazo and Müller, 2002). It is extensively interconnected with other cortical and subcortical areas, including nearly all regions of the parietal

cortex and temporal cortex, and prestriate cortex of the occipital lobe. Especially, the thalamus holds the largest input further bridging the prefrontal cortex to subcortical structures including the basal ganglia, brain stem nuclei and cerebellum (Gazzaniga et al., 2014). These connections are essential for the brain's top-down executive control and goal-directed behavior.

2.2.1 Working Memory

Working memory refers to the short-lived representation of task-relevant information (Diamond, 2013). Patricia Goldman Rakic calls it "the blackboard of the mind" (Goldman-Rakic, 1992) which vividly explains the role of working memory, i.e., to hold information online for current need. In a real situation, this online information may involve both memory from the past and interpretation of current states of the environment. For example, when we are waiting to pick up an old friend from the airport and looking for him/her from the crowd, we need to keep both the current goal and distant memory of his/her characteristics, e.g., appearance and height, in active working memory (Li et al., 2015).

Working memory provides an interface for higher level cognitive operations, cross-talking between attention, memory and executive functions (Cowan, 1999; Baddeley, 2003), Fig. 4. In Baddeley's model of working memory, four components are proposed, including a central EF, two short-term storage system (visuospatial sketchpad and phonological loop), and an episodic buffer (Baddeley, 2003). The central executive function is the most important component. It directs the two short-term storage systems and the episodic buffer which provides the interface for recruiting long-term memory. In contrast, Cowan's model of working memory tilts more toward the side of memory. Cowan refers to working memory as part of short-term memory and long-term memory which is activated by the focus of attention (Nelson, 1995).

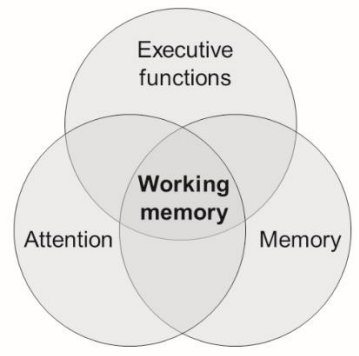

Figure 4. A schematic description of working memory as an interface between attention, executive functions and memory (Purdy, 2011).

Working memory essentially differs from other forms of memory in respect to its close association with the prefrontal cortex. The crucial role of the prefrontal cortex for working memory is seen in patients with prefrontal lesions leading to impaired recency-related working memory, i.e., the ability to temporarily segregate the timing or order of events. For example, a patient with frontal lobe syndrome fails to organize the action of cooking following a proper temporal sequence, although she is able to remember all ingredients and perform all actions (Jasper, 1995; Milner, 1995). These difficulties are likely to stem from both executive dysfunction and working memory deficits.

Working memory is important for even the simplest cognitive task. For example, in the Executive-RT task (see chapter 3.4), while instructed to indicate the orientation of the triangle (either upward or downward by pressing one of two buttons) subjects need to hold the orientation of the previously presented triangle in working memory for a correct response (Hartikainen et al., 2010b). Incorrect responses of the triangles' orientation may therefore represent impaired working memory function. Furthermore, this working memory task can be made more challenging by additional rules such as embedding it with Go/NoGo signals with changing rules and emotional distractors. While additional elements in the task might not specifically affect working memory function, increased consumption of attentional resources by rule switching and emotional distraction may further challenge working memory performance (Hartikainen et al., 2010b; Hartikainen et al., 2014).

2.2.2 Response Inhibition

Inhibition of inappropriate or irrelevant responses is a key element of the executive functions supporting flexible and goal-directed behavior (Verbruggen and Logan, 2008). One favorable approach to study response inhibition is the Go/NoGo paradigm (Logan, 1994). Occasionally, a NoGo signal appears among the Go signals requiring subjects to withhold prepotent responses, i.e., stopping instead of responding. A simple stopping response often consists of several cognitive functions, e.g., motor response, monitoring and adjusting, and inhibitory control. Therefore, a response inhibition process may engage several brain regions including the pre-supplementary-motor area (Xue et al., 2008), the ACC and right inferior frontal gyrus (Chevrier et al., 2007).

2.3 Theories of Emotion

Emotion refers to the short-termed psychophysiological reaction patterns as triggered by the surrounding stimuli (Clore and Ortony, 2000). Emotion may be recognizable in action tendency and/or physiological changes. Emotion is different from mood, the subjective feelings, by its relatively shorter duration and its relevance with exogenous stimuli (Ekman and Davidson, 1994). Basic emotions typically include anger, fear, sadness, enjoyment, disgust and surprise (Ekman, 1999).

2.3.1 Dimensions of Emotion

Study of even basic emotions is often complex. A simplified approach for studying emotions is to focus on two dimensions of the emotional stimuli, i.e., valence and arousal. Valence usually has three levels: positive, neutral, and negative. For example, a spider or a snake which generally leads to fear can be characterized as negative. A smiling face usually makes us happy and is regarded as positive. Those which do not often affect our emotion, such as a desk, are neutral. On the other hand, emotional stimuli with the same valence may lead to different arousal levels. For instance, a natural color picture of a toxic spider is likely to be more arousing than a schematic line-drawing spider. On the other hand, even a schematic line drawing of a spider coding evolutionarily relevant biological threat may be more arousing and efficient in activating the limbic circuits, including the amygdala, than social emotional stimuli

such as facial expressions. Thus, valence and arousal form the two dimensions of emotional stimuli.

Another way to study emotion is to measure how motivated an emotional stimulus makes a person to approach or to withdraw. As proposed by Davidson and his colleagues (Davidson et al., 1990; Davidson, 1992a), different emotional states can drive us to either approach or withdraw from the stimuli. For instance, fear makes us avoid the stimuli by withdrawing. In contrast, enjoyment tends to motivate us to approach stimuli. The concept of approach and withdrawal is nevertheless not a simple association with positive and negative types of valence. Anger, although a negative valence, can motivate us to approach instead of to withdraw. Hence, motivation may be considered another dimension of emotion. Davidson has also proposed a method for the evaluation of motivation, i.e., measure of cerebral alpha asymmetry which is talked later.

2.3.2 Generation of Emotion

The study of emotion has existed since the late 19th century. Charles Darwin compared the emotional expressions of man and animals and thought that emotions were often a collection of patterns of actions, e.g., baring the teeth for anger and tears representing upset. He proposed that emotions were similar across species. The pioneering work of Darwin on emotion has been recorded in the book "The Expression of the Emotions in Man and Animals, Darwin 1872".

Later, William James and Carl Lange provided the James-Lange theory stating that emotions were virtually the sets of bodily changes in response to emotive stimuli (James, 1884; Lange, 1885). James described what emotion was by using the example "fear while spotting a bear". He stated that, when we met a bear it was not that the feeling of fear was firstly generated and then we decided to run away, but rather that fear occurred the same time as we ran away. Therefore, James argued that "our feeling of the same changes as they occur is the emotion" (James, 1884).

The James-Lange theory was later challenged by Cannon and Bard. The Cannon-Bard theory (Cannon, 1927; Bard, 1928; Cannon, 1931) stated that physiological bodily responses could not differentiate the different states of emotion. Instead, they proposed that the neocortex generated emotional feelings while the periphery nervous system contributed to emotional reactions. They proposed a model of parallel brain processing which included a fast thalamo-cortical pathway in generating emotion and a slower thalamo-hypothalamus pathway in producing

emotional reactions. Bard also demonstrated that surgical separation of the neocortex from brain stem above the thalamus and hypothalamus in cats did not impair emotional reactions (Bard and Rioch, 1937). However, later findings that some emotional responses could be differentiated based on autonomic activity (Ekman et al., 1983) refuted part of the Cannon-Bard theory.

Other theories regarding the generation of emotion also exist. For example, LeDoux's high road and low road theory proposes that emotion is generated by two separate pathways: one fast way from thalamus to the amygdala and the other slow process from the thalamus to cortex and then to amygdala (LeDoux, 1996).

2.3.3 Neural Circuits Involved in Emotion

In 1937, a famous neuroanatomist James Papez proposed a neural circuitry of emotion known as the "Papez circuit" (Papez, 1937). This circuitry consists of brain structures including the thalamus, hypothalamus and the cingulate cortex. Papez proposed that sensory inputs into the thalamus were diverted to either streams of "thoughts" or streams of "feelings". For thought, the sensory input was conducted to cingulate cortex, further to the hippocampus, the fornix, mammillary bodies and back to the anterior thalamus. For feelings, the sensory information was transmitted via the anterior thalamus to the mammillary body and further to the cingulate cortex. Papez suggested that the cingulate cortex was the core for emotion.

After Papez' Circuit, Paul MacLean proposed the limbic systems which has become more broadly supported by current research (MacLean, 1949; Maclean, 1952). In comparision to the Papez Circuit, other important structures were added into the emotional system including the amygdala and PFC. The critical role of the PFC, especially the orbitofrontal cortex (OFC), in emotional regulation has been well demonstrated in the case of Phineas Gage. In 1848, Phineas Gage was hit by an iron rod which injured his forebrain by entering below the left eyebrow and exiting at the top of the skull. Thereafter, Gage turned to be a totally different person being impatient and easy to anger. Prefrontal damage induced emotional changes highlighting the importance of PFC in emotional processing (Macmillan, 2000).

The role of amygdala in emotion, especially in fear, was firstly recognized due to the finding that monkeys with bilaterally damaged temporal brain lobes showed a lack of fear (Klüver and Bucy, 1937). Later studies by Weiskrantz found that similar emotional changes were able to achieve with damage limited to the amygdalae highlighting the crucial role of amygdala in emotion (Weiskrantz, 1956). Current

neuroimaging studies have provided solid evidence for the engagement of amygdala in emotional processing (Vuilleumier et al., 2001; Pessoa et al., 2002).

2.4 Selective Attention

William James has described attention like this: "It is the taking possession of the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness are of its essence." (James, 1890). Attention has been one of the most popular construct in modern cognitive and affective science, psychology and related research fields.

Attentional recourses are thought to be limited (Broadbent, 1958; Wickens, 1991) constraining how many tasks can be successfully performed at the same time. Attentional allocation can be voluntarily controlled, such as imagining a beautiful scene or reading a book. Voluntary attention is under top-down control in a goal-directed behavior. Attention can also be passively attracted, i.e., involuntary attention such as when we hear the alarm ringing. Two neural networks have been included in different attentional functions. The dorsal fronto-parietal attention network, involving the intraparietal and superior frontal cortex, is recruited in goal-directed behavior (Corbetta and Shulman, 2002). The ventral fronto-parietal network, including the temporo-parietal and inferior frontal cortex, has been activated by unexpected or novel stimuli. The ventral attention network is thought to be right-lateralized (Corbetta and Shulman, 2002).

2.5 Emotion-Attention Interaction

Imagine that we are having coffee while reading a book on the balcony in a warm beautiful sunny day. All our attention has been spent in enjoying this beautiful moment and the stories from the book. Suddenly we see some spider webs at the corner of the wall and even a spider climbing on top. Immediately our attention is drifted due to the emotion of fear. However, it is just a small spider. We decide to continue this enjoyable moment and to forget the spider.

In this imagined situation, we can see an example of emotion-attention interaction. It includes an involuntary attentional drift due to the emotionally negative spider, and a voluntary attentional return to the previous cognitive tasks,

i.e., reading the book. Healthy emotional functions are characterized by balanced control between voluntary attention allocation to the current goals and involuntary attention allocation to emotional stimuli such as potential threat. Altered emotion-attention interaction has been proposed as a marker for brain disorders (Beard, 2011) and it has been extensively studied using experiment paradigms including detection, search, masking, attentional blink and interference (Oliveira et al., 2013).

2.5.1 Attentional Bias to Emotional Stimuli

The prioritized access of emotional stimuli to attention has been demonstrated by Hartikainen et al (2000) and later confirmed by other studies (Vuilleumier et al., 2001; Vuilleumier and Schwartz, 2001; Pessoa et al., 2002). In visual attention studies, it is shown that task-irrelevant emotional stimuli compete for attentional resources with task-relevant targets reflected in interference of cognitive performance and diminished target-evoked ERPs (Hartikainen et al., 2000; Hartikainen et al., 2007; Hartikainen et al., 2010a). Specifically, reduced attentional allocation to targets in the context of emotional stimuli has been supported by slowed reaction times (RTs) and reduced right parietal N2-P3 peak-to-peak amplitudes. In these studies, Hartikainen et al. (2000, 2007, 2010a) have used either emotional stimuli from the international affective picture system (IAPS) or schematic line-drawing images with the shape of spiders or flowers. Interestingly, the effects of attentional competition have been pronounced over the right hemisphere, interfering with targets predominantly processed by the right hemisphere, i.e., left visual field targets (Hartikainen et al., 2007). Further evidence for predominantly right hemispheric emotion-attention interaction was obtained by unpleasant emotional distractors interfering with processing of global visual features in contrast to local visual features (Hartikainen et al., 2010a) and interrupting response inhibition (Hartikainen et al., 2012b), i.e., functions mainly relying on the right hemispheric networks.

Unpleasant emotional stimuli temporarily interfering with attention to left visual hemifield in healthy subjects (Hartikainen et al., 2000; Hartikainen et al., 2007) resembles neglect syndrome where right hemispheric lesion leads to impaired attention to the left visual hemifield (Mesulam, 1981). On the other hand, neurological patients with neglect have been shown to detect more frequently threat-related emotional stimuli in comparison to emotionally neutral control stimuli in their neglected left hemifield further supporting prioritized access of emotional stimuli to attention networks (Vuilleumier and Schwartz, 2001).

Biased attention allocation to emotional stimuli is also seen in impaired executive functions due to emotional distractors (Hartikainen et al., 2012b). Using the Executive-RT test (detailed description of the test can be found in chapter 3.4), Hartikainen et al. (2012b) demonstrate that emotional distractors lead to increased commission errors indicating impaired response inhibition in young healthy subjects. Instead of using IAPS images, the Executive-RT test uses line-drawings of affective images with minimal visual-feature difference and any configurational difference attributed to emotional value (Vuilleumier and Schwartz, 2001).

Attentional bias to emotional stimuli is also observed in studies using attentional blink paradigms. When successive presentations of stimuli are given, the second stimulus immediately presented after the first one is often neglected due a lag period which is called the attentional blink. However, emotionally arousing word stimuli, either positive or negative, can overcome attentional blink thus affecting perceptual processing (Anderson, 2005).

Attentional bias to emotional stimuli, especially to those that are fear-related, is biologically crucial for survival (Öhman et al., 2001). Fast and automatic processing of emotional threating stimuli is one of the key properties of the limbic system (Öhman, 2005). In addition to the limbic system, emotional stimuli specifically activate vast brain regions such as the orbital gyrus, inferior and superior parietal lobule, and fusiform gyrus (Lang et al., 1998). While these brain regions are also involved in normal cognitive functions, simultaneous or temporally overlapping engagement in emotional responses may lead to emotion-attention interaction, like what happened in dual cognitive tasks (Klingberg and Roland, 1997). The phenomenon of emotion-cognition interaction has been typically shown in cognitive tasks with emotional interference, where emotional distractors interfere with the following cognitive performance (Hartikainen et al., 2000). Several brain regions that are involved in emotion-attention interaction have been demonstrated using neuroimaging approaches (reviewed below).

2.5.2 Neural Circuits underlying Emotion-Attention Interaction

Prioritized access of emotional stimuli to attention is associated with the function of subcortical areas including the amygdala (Anderson and Phelps, 2001). The visual processing of emotional information through the retina-thalamus-amygdala pathway is fast (LeDoux, 1996). Early neuroimaging studies demonstrate that the amygdala is activated by masked presentation of fearful facial expression (Morris et al., 1998;

Whalen et al., 1998). In these studies, fearful faces are presented shortly (~30 ms) and immediately masked by neutral faces. Subjects report that they do not see the fearful faces while a significantly increased activity at amygdalae is found. Also, Vuilleumier et al. find that the amygdala is activated by emotional facial expressions independent of whether the emotional stimuli are attended or not (Vuilleumier et al., 2001).

However, Pessoa et al. have investigated the influence of attention on the processing of facial expression by the amygdala and find that emotional stimuli do not activate the amygdala when attentional resources are exhausted (Pessoa et al., 2002). Pessoa et al. also use a visual attention task with three-level attentional loads, easy, medium and hard, and find that task-irrelevant fearful facial expressions lead to elevated amygdala activity only when the task is easy but not when it is medium or hard (Pessoa et al., 2005). They argue that higher task load leads to exhausted attentional resources and thus no activation is found in amygdala even with emotional distraction. The proposal that exhausted attentional resources prevent emotional interference may be true in specific situations and with some emotional stimuli.

In our lab, it has been shown that negative emotional stimuli interferes with performance speed during high load cognitive tasks (Mäki-Marttunen et al., 2014). Specifically, in a visual attention task Mäki-Marttunen et al. find that unpleasant emotional distractors lead to increased RTs only when task load is high but not when it is low. The discrepancy between these findings may derive from variable factors including the involved population groups, the cognitive tasks, the types of emotional stimuli and their relation to the task. Facial expression are not high-threat biologically relevant emotional stimuli supporting survival and their processing may be influenced by the available attentional resources. In contrast, task-irrelevant threat-related stimuli such as line-drawings of spiders have been found to interfere with both performance speed and accuracy in both healthy and patient groups during high-load cognitive tasks (Hartikainen et al., 2010b; Hartikainen et al., 2012b; Hartikainen et al., 2014; Sun et al., 2015).

In addition to the involvement of the amygdala, both Vuilleumier and Pessoa report an attention-dependent emotional responses at the right OFC and ACC (Vuilleumier et al., 2001; Pessoa et al., 2002). Specifically, the ACC and right OFC are only activated when emotional facial expressions are attended. When face stimuli are task-irrelevant, fMRI does not reveal any difference between fearful and neutral faces for the activity of these structures. Hartikainen et al. (2003, 2012a) on the other hand has shown the importance of OFC in allocating attention to emotionally

relevant stimuli. Patients with lesion to the OFC fail to allocate additional resources to task-irrelevant emotional IAPS images like healthy subjects do and instead allocate additional resources to task-relevant stimuli. The balance between voluntary and involuntary attention seems to be shifted towards voluntary attention in patients with orbitofrontal lesion (Hartikainen et al., 2012a).

Both imaging and ERP studies point to the importance of the right fronto-parietal attention networks in emotion-attention interaction. Hartikainen et al. (2000, 2007, 2010a) have shown that emotional distractors compete for attentional resources leading to interference of especially right hemisphere dependent cognitive performance. The involvement of the right fronto-parietal attention networks in emotion-attention interaction has also been shown with fMRI study where unpleasant emotional stimuli interfere with task-related right fronto-parietal network activation especially when top-down attentional control is low due to low task load (Mäki-Marttunen et al., 2014).

In summary, neural circuits underlying emotion-attention interaction involve, but are not limited to, the amygdala, OFC, ACC and the dorsal and ventral attention networks.

2.5.3 Emotion-Attention Interaction and Brain Disorders

Alterations in emotion-attention interaction are observed in many psychiatric and neurological disorders including anxiety or depression, or injury to parts of the neural circuits important for this interaction such as OFC damage or mild traumatic brain injury (MTBI). An appropriate balance between attention allocation to current goals and to emotionally significant stimuli such as threat is a prerequisite for adaptive behaviors and euthymic mood.

Anxiety has been characterized with increased attention allocation to emotional stimuli (Mathews and MacLeod, 1994). In experimental tasks, anxiety states usually lead to slowed performance due to emotional distractors but speeded performance when the emotional stimuli are targets. For instance, subjects with either current or recovered anxiety demonstrate slowed performance in a target-searching task with the presence of threat-related stimuli than healthy subjects (Mathews et al., 1990). In contrast, when emotional stimuli are the targets, increased detection speed is reported in patients with anxiety (MacLeod et al., 1986). However, associations between the vast experimental findings and clinical anxiety are in complicated models (Mathews and Mackintosh, 1998). Individuals with low trait anxiety only

show attentional bias to highly threating stimuli while ignoring those with low threat value. In contrast, patients with high trait anxiety have biased attention toward threat-related stimuli with both high and low threat value. Thus, it is thought that only biased attention toward low threat value stimuli may be associated with anxiety-proneness (Mogg and Bradley, 1998).

Neurocognitive mechanisms of anxiety have been linked with the amygdala-prefrontal circuity (Bishop, 2007). Attentional bias to emotional stimuli has been linked with amygdala hyperactivity. For example, increased amygdala activity upon the exposure to negative stimuli has been found in patients with generalized social phobia compared to healthy subjects (Phan et al., 2006). On the other hand, high anxious individuals demonstrate lower prefrontal recruitment than those with low trait anxiety (Bishop et al., 2004). Explicitly, compared to healthy subjects, Bishop et al. find that individuals with high anxiety levels have reduced activity at the rostral ACC and lateral PFC in a cognitive task with threat-related distractors.

Like anxiety, depression has also been associated with negativity bias and dysregulated amygdala-prefrontal circuit. For example, patients with depression easily pay attention to socially threating words, while those with anxiety are attentive to physically threating stimuli (Mathews et al., 1996). When emotional stimuli are processed, patients with depression demonstrate increased activity in the amygdala compared to control subjects (Sheline et al., 2001). Furthermore, depression has also been associated with increased limbic activity, including the subgenual cingulate and anterior insula, and decreased activity in the neocortical regions involving the right dorsolateral prefrontal and inferior parietal cortices (Mayberg et al., 1999).

Mild traumatic brain injury (MTBI) may disrupt the fronto-striatal networks leading to impaired executive functions (Hartikainen et al., 2010b) and altered emotion-attention interaction (Mäki-Marttunen et al., 2015). MTBI has been linked with vulnerability to depression and enhanced allocation of attention to threat seen in both behavior and electrophysiology (Mäki-Marttunen et al., 2015). Mäki-Marttunen et al. speculated that the prefrontal cortex is susceptible to injury and the inefficiently functioning frontal circuits may be responsible for reduced top-down control of emotional response leading to enhanced attention allocation to threat, and this potentially contributes to susceptibility to depression in this population.

2.6 Relevant Cognitive Neuroscience Methods

2.6.1 Reaction Time Studies

Reaction time is a sensitive indicator of the underlying mental processes and provides rich information on the temporal organization of mental activities (Sternberg, 2004). As Jastrow pointed (Jastrow, 1890),

"the study of the time relations of mental phenomena is important from several points of view: it serves as an index of mental complexity, giving the sanction of objective demonstration to the results of subjective observation; it indicates a mode of analysis of the simpler mental acts, as well as the relation of these laboratory products to the processes of daily life; it demonstrates the close inter-relation of psychological with physiological facts, an analysis of the former being indispensable to the right comprehension of the latter."

Although RT itself may contain important information in psychological experiments, the experimental variables and the modulated mental processes are what we study in the current thesis. In the Executive-RT test (see chapter 3.4), experimental variables include neuromodulation statuses and emotional distractors with different valences. RTs are merely the measurable indicators for these cognitive modulations. For example, cognitive processing of emotional distractors under different neuromodulation status are reflected in RT changes, indicating the influence of neuromodulation on emotional reactivity (Hartikainen et al., 2014; Sun et al., 2015).

2.6.2 Event-related Potentials

Electroencephalography refers to the measurement the electrical activity of the brain by placing electrodes on the scalp. The electrical signals are recorded, amplified and plotted with high temporal resolution. Raw EEG signals are noise-dominated and represent a mixture of brain responses from many neuronal resources. However, embedding EEG with specific and repetitive cognitive events plus a simple averaging technique allows to extract specific brain responses from EEG signal and these brain responses are known as the event-related potentials (ERPs) (Luck., 2005). ERPs are thought to represent a summation of postsynaptic potentials of many neurons and are associated with specific cognitive, sensory or motor events.

An ERP waveform is characterized with a sequence of negative and positive deflections, known as components, peaks or waves. Negative-going or positive-going components are traditionally denoted with N or P, e.g., P3 refers to a positive peak typically emerging 300 ms post-stimuli (Patel and Azzam, 2005; Polich, 2007).

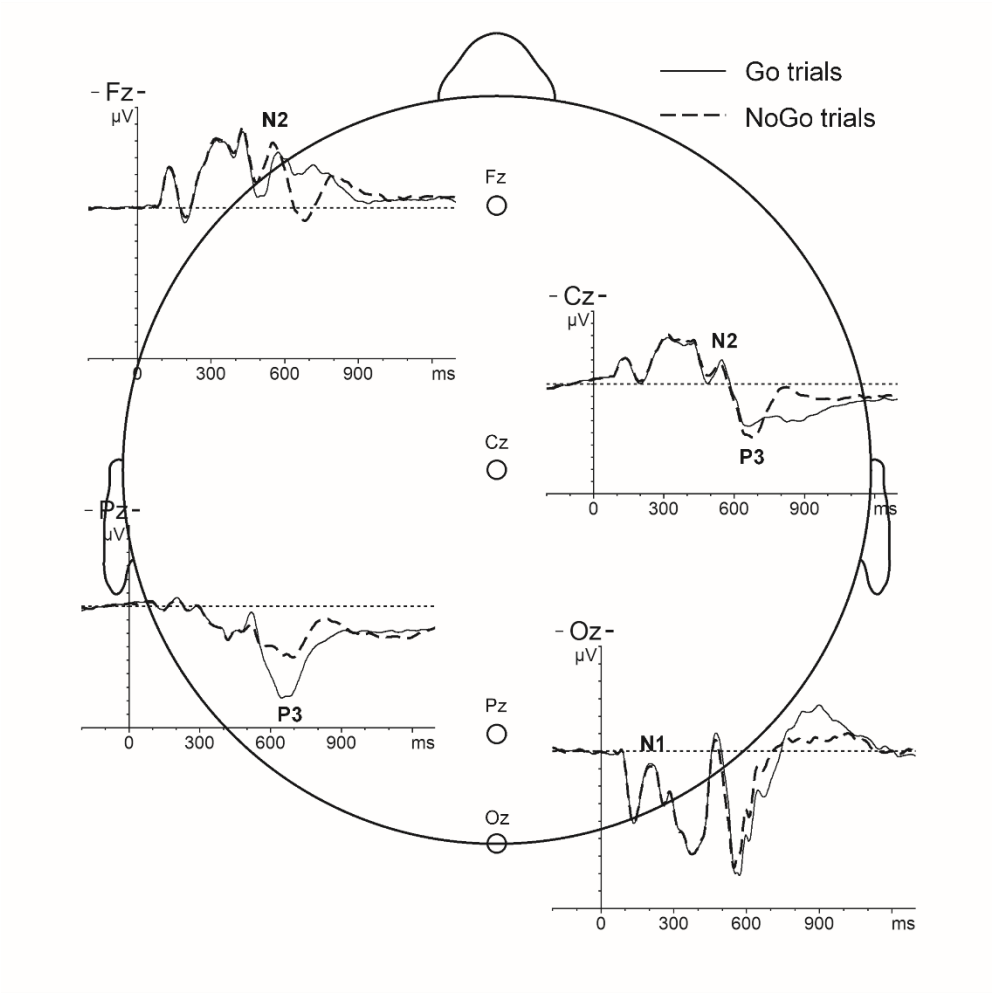

Figure 5. Midline ERPs of healthy subjects during the Executive-RT test. ERPs for Go and NoGo responses are demonstrated separately. Within each response type, ERPs are generated by averaging all segments. Common reference is used.

2.6.2.1 Visual N1

The visual N1 is a negative component which typically peaks at around 150 to 200 milliseconds post-stimulus. The parieto-occipital N1 amplitude is linked with visual attention with larger N1 amplitude indexing greater visual attention (Mangun and Hillyard, 1991; Hillyard and Anllo-Vento, 1998; Luck and Ford, 1998). For instance, in a visual attention task where subjects are cued to attend to target stimuli, increased parieto-occipital N1 amplitude is found when the target stimuli are attended compared to when they are not attended (Mangun and Hillyard, 1991). The N1 usually has a contralateral distribution to the visual field of the stimulus if the stimuli are presented laterally and a bilateral distribution to centrally presented stimuli (Makeig et al., 1999).

2.6.2.2 P3

The P3 or P300 is firstly reported in a study by Sutton et al with the amplitude of a positive-going component peaking at around 300 ms linked to stimulus uncertainty (Sutton et al., 1965). The exact principle of how and why the brain generates P3 remains elusive (Luck., 2005). Studies have uncovered several distinguishable components of P3 wave, including a frontally maximal P3a and parietally maximal P3b (Courchesne et al., 1975; Squires et al., 1975). Possibly, the initial appearance of the novel stimuli bring a strong context updating generating a frontally distributed P3a component, while its repetitive presentation giving a shifted maximal P3b component (Courchesne, 1978; Friedman and Simpson, 1994).

The neural origins of P3 have been illustrated with brain lesion studies and neuroimaging evidences. Brain lesion studies demonstrate the critical role of temporo-parietal, frontal and limbic areas in generating P3 (Knight et al., 1989; Soltani and Knight, 2000), which are also confirmed by neuroimaging studies, for example (Opitz et al., 1999). Further, different types of salient sensory inputs, whether auditory, visual or tactile, uniformly activate brain regions including the temporo-parietal junction, insula, left cingulate, inferior frontal gyrus and supplementary motor area, indicating the potential role of these attentional and limbic brain networks in P3 generation (Downar et al., 2000).

The amplitude of P3 has been thought to index attentional resources (Kok, 1997; Polich, 2007). For instance, in a dual task reduced attentional resources in the primary task due to attentional engagement by a secondary task lead to reduced P3 amplitude (Isreal et al., 1980). Furthermore, studying words with full attention leads

to greater P300 amplitude along with better word recognition in comparison to studying with divided attention (Curran, 2004).

2.6.3 The N2-P3 Complex

A negative ERP deflection precedes the positive P3 peak around 200 ms post-stimuli and is known as the N2 or N200. The N2 has been found in all kinds of cognitive tasks with its timing and distribution dependent on the task (Luck., 2005). The difference amplitude between the negative N2 and the positive P3, i.e., N2-P3 peak-to-peak amplitude, is thought to index attentional resource allocation (Daffner et al., 1998). The N2-P3 peak-to-peak amplitude has been used as an index of attentional resources in our previous studies (Hartikainen et al., 2007; Hartikainen et al., 2010a, 2012a; Mäki-Marttunen et al., 2015). While the amplitudes of single ERP peaks are typically referenced to the ERP baseline, peak-to-peak measure of amplitude between neighboring ERP components may be a more robust measure in clinical populations allowing for better control of the influence of EEG slow waves. This is especially beneficial when analyzing ERPs in neurological patients such as patients with epilepsy where prominent pathological EEG oscillations or slow waves may influence ERP peak amplitudes (Sun et al., 2015).

2.6.4 Frontal Alpha Asymmetry

A motivational system, i.e., the approach and withdrawal system, has been proposed for frontal lobe functions (Davidson, 1992b). The measure of frontal alpha asymmetry derives from Davidson's approach and withdrawal theory of emotional responses (Davidson et al., 1990; Davidson, 1995). Relatively higher right than left frontal activity has been linked to increased withdrawal motivation while relatively higher left than right frontal activity indexes increased approach motivation. Typically, the level of frontal alpha power is inversely linked with the intensity of cognitive activity, i.e., greater frontal activity is indicated by less alpha power (Davidson, 1988). Increased right-sided frontal alpha symmetry during both resting state and cognitive tasks has been linked with a predisposition of psychopathology such as depression and anxiety (Gotlib, 1998; Davidson et al., 2002; Mitchell and Possel, 2012; Stewart et al., 2014).

2.7 Epilepsy, Human Cognition and Emotion

2.7.1 Epileptic Seizures and Epileptic Syndromes

Epilepsy refers to a heterogeneous group of neurological disorders characterized by spontaneous occurrence of seizures along with changes in neurobiologic, cognitive, psychological, and social conditions (Fisher et al., 2005). Epileptic seizures result from electric discharges in a cluster of hyper-excitable neurons typically from the cortical and hippocampal structures. The etiology of epileptic seizures are diverse, with a large portion being intractable. Epileptic seizures are classified based on sites of origin, discharge propagation and time course, with two main categories - generalized and focal seizures (Blume et al., 2001; Fisher et al., 2005).

Several factors contribute to epileptic syndromes including seizure types, EEG changes, age-specific factors and brain's structural changes (Fisher et al., 2005). Similarly, two main categories of epileptic syndromes exist, the generalized and focal epilepsy which are further divided into different subtypes. Epileptic syndromes largely determine the choice of treatment methods, including medication and possible surgical treatments. Around one third of diagnosed epilepsy is uncontrolled with antiepileptic drugs (AEDs) and epilepsy can be thought refractory due to failure of seizure control after at least two rounds of AEDs (Arroyo et al., 2002).

2.7.2 Epilepsy and Brain Plasticity

Solid evidence from studies using epileptic animal models have demonstrated that epilepsy leads to neural loss, neurogenesis, axonal sprouting, dendritic changes and changed gene expression (Pitkänen and Sutula, 2002). Progressive seizure-induced brain plasticity in rats is reported to cause cognitive decline (Sutula et al., 1995). In humans, neural loss especially in the hippocampal areas, have been found due to progressive epilepsy (Dam, 1980; Mathern et al., 2002). The amygdala and entorhinal regions are also reported as major targets for epilepsy-induced neural damage in patients with temporal lobe epilepsy (Yilmazer-Hanke et al., 2000; Salmenpera et al., 2001). Epilepsy-induced neural damage may potentially lead to altered cognitive and emotional functions.

2.7.3 Epilepsy and Cognition

The effects of epilepsy on human cognition are heterogeneous depending on diverse features including the causes of epilepsy, pathologic mechanisms, topography of epileptogenic foci and the clinical courses (Elger et al., 2004; Hermann et al., 2010).

Patients with easily controlled generalized epilepsy demonstrate slightly deteriorated cognitive function. For example, patients with generalized epilepsy are reported to have impaired working memory with reduced frontal lobe functioning during working memory performance (Swartz et al., 1996). Also, patients with generalized epilepsy have impaired memory, illustrated by poor performance in California Verbal Learning Test, and attentional deficits in a WISC-R digit span and coding test (Mirsky et al., 2002).

Focal epilepsy, such as the temporal lobe epilepsy (TLE), usually has location-related cognitive deficits associated to functions of the respective brain areas. For instance, TLE is often accompanied with hippocampal sclerosis and given the critical role of hippocampus and its associated networks in episodic declarative memory, TLE is often complicated with memory related problems. This is exemplified in patients where left-sided TLE leads to verbal memory deficits (Helmstaedter et al., 1997; Hermann et al., 1997). Patients with frontal lobe epilepsy demonstrate miscellaneous aspects of cognitive dysfunctions depending on the affected subsections in the frontal lobe (Helmstaedter et al., 1996; Exner et al., 2002).

2.7.4 Epilepsy and Emotion

Chronic epilepsy, especially TLE, has been associated with emotional disorders such as depression (Lambert and Robertson, 1999). In line with these clinical findings, TLE has been linked with neural loss, neurogenesis, axonal sprouting and dendritic changes at the temporal limbic area (Pitkänen and Sutula, 2002). Epilepsy-induced changes in brain plasticity may lead to depression-related symptoms via a variety of pathological approaches including the altered orbitofrontal functions (Salzberg et al., 2006).

Behavioral evidence has shown that temporal lobe epilepsy, especially right mesial temporal lobe epilepsy, leads to reduced amygdala activity and impaired emotional response to fearful faces (Meletti et al., 2009; Toller et al., 2015). Given the critical role of mesial temporal lobe, e.g., amygdala, in emotions, impaired facial emotion recognition is probably linked with medical temporal dysfunctions due to TLE-caused neural damage in this brain region (Meletti et al., 2003; Meletti et al., 2009).

3 Material and Methods

3.1 Ethical Issue

All subjects provided their written consents for participation in the studies. All studies were approved by the local ethical committee of Tampere University Hospital.

All the studies were conducted in the Behavioral Neurology Research Unit of Tampere University Hospital. The unit was established by Dr. Kaisa Hartikainen with funding from the Academy of Finland and Tampere University Hospital in 2012. The unit is located at the hospital campus (Finmed 6-7) and belongs to the Pirkanmaa Hospital District, allowing access to patient populations with refractory epilepsy treated with DBS and VNS. The Behavioral Neurology Research Unit has a strong research team involving neurologists, neurosurgeons, engineers and medical students. We use behavioral approach, i.e., the Executive-RT test, and electroencephalography to investigate the effects of neuromodulation on human cognition and emotion. The Executive-RT test sensitively measures subtle changes in human executive functions. While EEG provides valuable information on the attentional mechanism of cognitive performance. Thus, the facilities, expertise and methodology were ethically solid for the conducted studies.

ANT-DBS has been approved for treating refractory epilepsy in Europe since 2010. However, knowledge of the mechanism of its action is limited. While it efficiently reduces seizure frequency, patients with this treatment may suffer from memory and depression-related symptoms. Therefore, optimized ANT-DBS treatment calls for deeper understanding of how ANT-DBS affects human cognition and emotion. With the help of neurosurgeons and neurologists, we studied the effects of ANT-DBS on human executive functions while the stimulation was on and while it was off. During the experiment, patients' EEG were carefully monitored and their behavior monitored with a video camera. In patient studies there was always a neurologist present to attend to the well-being of the patient. We minimized all potential harms to patients by limiting the continuous stimulation ON and OFF periods. In order to avoid long periods without stimulation, ON and OFF periods were not randomized. Also the stimulation parameters were within the parameter

settings that did not differ substantially from clinically used parameters. Patients could choose to quit whenever they felt uncomfortable or unwilling to continue the study. The study would provide invaluable knowledge that helps to optimize the treatment in the future.

VNS has been used for treating refractory epilepsy and severe depression. Exact mechanism of VNS is still under investigation. VNS treatment for epilepsy often leads to subjectively reported mood and cognitive improvement. However, objective measures of the chronic effects of VNS on cognition and emotion remains controversial. We used a sensitive behavioral test with electrophysiological measure to investigate the immediate and direct effect of VNS on human executive functions. Our study will not only provide clinical significance by also holds methodological merits.

In addition to the clinical benefits, these studies also bears neuroscientific significance in aiming to deepen the understanding of the human brain functioning. For instance, ANT-DBS allows us to study the specific role of ANT in human emotion-attention interaction, adding novel insights on human brain circuits. Also, we studied the potential extraocular light sensitivity of the human brain with the help of volunteered healthy subjects. While participation in the study may not lead to immediate benefits for the volunteers, these studies aimed to provide invaluable knowledge on brain functions and circuits and the impact of neuromodulation on them that helps develop and optimize neuromodulatory treatments in the future. Therefore, in-depths knowledge of brain functioning provides far-reaching scientific, clinical and societal benefits, making the efforts and investments to this research ethically justifiable.

3.2 Subjects

The following groups of subjects are involved in the listed publications (Table 1).

Table 1. Subjects involved in the listed publications.

Publications	Subjects	Age and sex
I	12 patients with ANT-DBS for treating epilepsy	32.7 ± 9.4 years old; 8 male and 4 female
II	6 patients with ANT-DBS treatment, while having proper ANT location and analyzable ERPs (Subgroup of subjects in Article I)	37 ± 13 years old; 3 male and 3 female
II	20 patients with VNS for treating epilepsy.	45 ± 13 years old; 12 male and 8 female
IV	18 healthy subjects with extraocular photomodulation	25 ± 6 years old; 3 male and 15 female

3.2.1 Patients with ANT-DBS

DBS at the ANT has been approved for the treatment of epilepsy in Europe since 2010. All patients were treated in Tampere University Hospital. Thirteen patients treated with ANT-DBS for refractory epilepsy participated in this study. Their clinical information is presented in Table 2.

The thirteenth patient joined this study after the publication of Article I. Therefore, his data were only included in Article II.

Table 2. Patients with ANT-DBS treatment.

Patient ID	Age/ Gender/ Hand used	Age at Diagnosis	Types of Epilepsy	Medication
P01	31/M/R	11 y	Occipital	Carbamazepine, Clobazam
P02	27/F/R	7 y	Temporal	Oxcarbazepine, Clobazam, Zonisamide
P03[a,e]	34/F/R	1.5 y	Frontal	Phenytoin, Clonazepam
P04	32/F/R	28 y	Multifocal	Clobazam, Zonisamide, Lacosamide
P05	24/F/R	16 y	Multifocal	Oxcarbazepine, Topiramate, Clobazam, Levetiracetam
P06[a,e]	23/M/R	11 y	Multifocal	Sodium valproate
P07[p,e]	48/M/R	8 y	Frontal	Carbamazepine, Zonisamide, Clobazam
P08[p]	25/M/R	10 y	Multifocal	Zonisamide, Clobazam, Valproic Acid, Lamotrigine
P09[p,e]	44/M/R	7 m	Frontal	Oxcarbazepine, Levetiracetam, Lacosamide, Citalopram
P10[p]	49/M/L	12 y	Temporal	Oxcarbazepine, Clobazam, Lacosamide
P11[p]	24/M/R	19 y	Frontal	Oxcarbazepine, Topiramate, Levetiracetam
P12[e]	31/M/R	25 y	Occipital	Carbamazepine, Clobazam
P13	57/M/R	15y	Multifocal	Oxcarbazepine

[p] = patients with poor performance; [a] = patients with no ANT locations;

[e] = Patients with unidentifiable ERP peaks.

3.2.2 Patients with VNS

Twenty patients with VNS treatment for refractory epilepsy participated the study. Their clinical information are listed is presented in Table 3.

Table 3. Patients with VNS treatment.

Patient ID	Age (y)/ Gender/ Hand used	Age (y) at Diagnosis	Types of Epilepsy	Medication
V01	29/F/R	25	Multifocal	Levetiracetam, Oxcarbazepine, Zonisamide
V02	32/F/ R	22	Temporal	Escitalopram, Lamotrigine, Lacosamide, Zonisamide
V03	35/M/ R	17	Frontal	Levetiracetam, Oxcarbazepine, Lacosamide, Zonisamide
V04[p]	41/M/ R	3	Multifocal	Deprakine, Vigabatrin, Topiramate, Olanzapine
V05	61/F/ R	9	Parietal	Lamotrigine, Zonisamide,
V06	46/M/ R	5	Temporal	Escitalopram, Clobazam, Carbamazepine, Lacosamide
V07[p]	36/F/ R	25	Multifocal	Quetiapine, Lamotrigine, Mirtazapine, Quetiapine, Lacosamide, Zonisamide
V08	50/M/ R	1	Multifocal	Perampanel, Lacosamide
V09	34/M/ R	8	Temporal	Deprakine, Levetiracetam, Lamotrigine, Zonisamide
V10	61/M/L	1	Temporal	Pregabalin, Lacosamide, Eslicarbazepine acetate
V11[e]	53/F/ R	19	Temporal	Carbamazepine, Zonisamide
V12[p]	70/M/ R	2	Multifocal	Gabapentin, Lacosamide
V13	32/F/L	16	Multifocal	Clobazam, Lamotrigine, Zonisamide
V14	34/F/ R	13	Fronto-temporal	Carbamazepine, Lacosamide, Pregabalin, Perampanel
V15	50/F/ R	9	Multifocal	Topiramate, Deprakine, Clobazam
V16	58/M/ R	18	Fronto-temporal	Carbamazepine, Clobazam
V17	47/M/ R	46	Temporal	Oxcarbazepine
V18	35/M/ R	20	Fronto-parietal	Lamotrigine, Deprakine, Perampanel, Clobazam
V19	37/M/ R	27	Multifocal	Levetiracetam, Oxcarbazepine
V20	64/M/ R			

[p] = patients with poor performance; [e] = Patients with unidentifiable ERP peaks.

3.2.3 Healthy Subjects with Extraocular Photomodulation

Eighteen young healthy subjects, convenience sample, volunteered in the test for studying the effect of extraocular light on human cognitive and affective functions. Recordings were performed during September and October 2012.

3.3 Neuromodulation Protocol

3.3.1 Stimulation Protocol of ANT-DBS

DBS electrodes (Medtronic 3389, Medtronic, Inc.) were implanted by neurosurgeons at the Tampere University Hospital for the treatment of refractory epilepsy. In the experiment, bipolar stimulation of deep brain structures instead of the monopolar stimulation was used. This allows to more precisely target the stimulated brain area and better control the electrical interference on EEG signals (Frysinger et al., 2006). In bipolar mode, two adjacent contacts of the implantable pulse generator (IPG) leads were used, with one being negative and the other positive contact. Also, in the experiment the neuromodulation mode of electrical pulses were continuous for roughly six minutes instead of intermittent stimulation, e.g., one minute ON and five minutes OFF, which is common in clinical settings. During the stimulation, a constant current of 5 mA was applied and the pulse frequency was 140 Hz.

Each IPG lead has four potentially active contacts. Out of these four contacts, we chose two contacts setting one positive and the other negative. Each time, one targeted brain area was stimulated by choosing the closest two contacts. When ANT was stimulated, the two contacts located in or closest to ANT were active contacts. In contrast, when the control location (which was called OA in article I and control location in article II) was stimulated, the furthest two contacts away from ANT were active. These control locations are typically more inferior toward the medial thalamus.

During the Executive-RT test, electrical stimulation was turned ON or OFF either at the ANT or at the control location. The starting locations were balanced among subjects. However, stimulation was always ON prior to OFF stimulation. Each stimulation status allows the subject to finish two blocks of the Executive-RT test (Fig. 6). Each block lasts for 128 seconds.

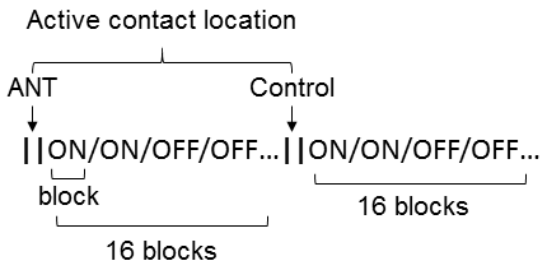

Figure 6. The stimulation protocol of ANT-DBS (Sun et al., 2015).

3.3.2 Stimulation Protocol of VNS

VNS was either administrated with VNS ON (cycling of 30s ON and 48s OFF with current 1.5 mA ~ 1.75 mA) or VNS OFF (current = 0 mA) while patients performed the Executive-RT test. There was a four-minute resting state before each session of behavioral tests allowing for sensory habituation (Fig. 7). With VNS either ON or OFF, subjects performed four blocks of Executive-RT test before the next session.

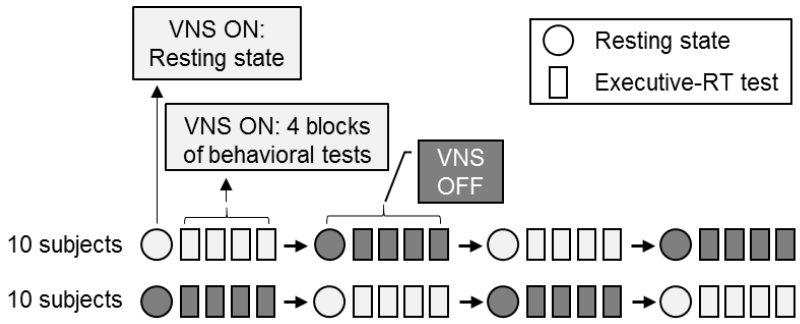

Figure 7. Stimulation protocol of VNS (article III).

3.3.3 Stimulation Protocol of Extraocular Photomodulation

During the test, bright light was either delivered (light ON) or not delivered (light OFF) alternatively. Before and after the session of behavioral tests, four blocks of resting state with each block lasting for three minutes were given. During the behavioral test, each status of extraocular photomodulation was sustained until the subjects finish two blocks of Executive-RT test.

3.4 Behavioral Test

The Executive-RT test (Fig. 8) is a computer-based visual attention Go/NoGo task with emotional distractors embedded in the Go/NoGo signal. During the test, scalp EEG was recorded.

The test was conducted in a sound-attenuated room with controlled light condition. During the test, subjects sat in front a 21" computer screen and the distance between the chair and the computer was fixed at one meter. The behavioral paradigm was presented using Neurobehavioral System Presentation software (Inc., Berkeley, CA, USA). The overall test lasts around 1.5 to 3 hours depending on the number of blocks of tests.

Each test block consisted of 64 two-second trials. The onset of each trial was a triangle pointing either up or down for 150 ms. Following the triangle a black fixation cross lasting for 150 ms was presented before the Go/NoGo signal – a stimulus in the form of a traffic light which was also presented for 150 ms. The color of the traffic light tells whether it is a Go or NoGo trial. The response rules were changed alternatively, i.e., a red light being a NoGo signal will be a Go signal in the next block of test. In a Go trial, subjects need to press one of the two buttons using their index (down button) or middle finger (up button) to indicate the orientation of the triangle. In a NoGo case, no button press is allowed.

In the middle circle of the traffic light, there was a distractor with schematic line drawing of either a spider or a flower. The spider and flower were composed of the same line elements only rearranged into their respective shape. This was done to minimize other visual features. The spider distractor conveyed threat-related information while a flower shaped configuration as an emotionally neutral control stimulus. Similar schematic drawings of a spider has been shown to activate human attentional networks and affect behavior (Vuilleumier and Schwartz, 2001).

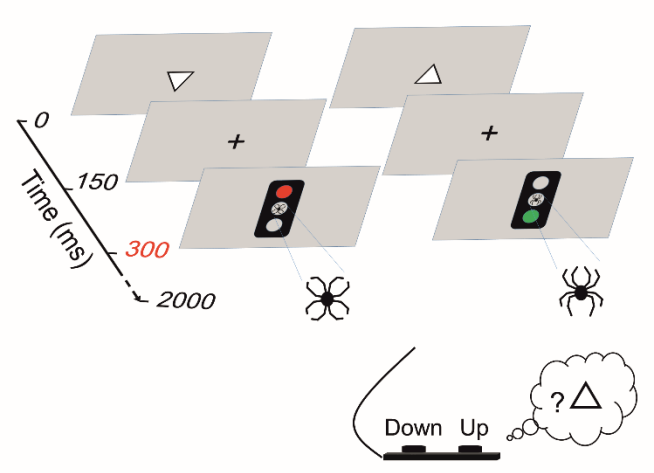

Figure 8. The Executive-RT test.

Behavioral outcomes of the Executive-RT test include RTs and errors. In RTs, only RTs with a correct button presses are analyzed. Three types of errors were generated: incorrect button presses, misses and commission errors. Incorrect button presses refer to an incorrect indication of the triangle's orientation in Go trials. Misses refer to no button press in Go trials. Commission errors include any button press in NoGo trials. In general, incorrect button presses are thought to reflect failed working memory performance, misses indicate difficulty in initiation or lapse in attention, and commission errors reflect impaired response inhibition.

3.5 Event-related Potentials

EEG was recorded at a sampling rate of 500 Hz using Brain Products actiCAP with 64-channel Ag/AgCl electrodes (Gilching, Germany). QuickAmp EEG amplifier was used to amplify the EEG signal. Offline EEG signals were analyzed using Brain Analyzer 2 software (Brain Products GmbH, Germany). Standard steps of ERP analysis are listed below:

a. Down-sampling to 250 Hz (purposed to speed up the processing).
b. Ocular correction (temporal independent component analysis by extended Infomax algorithm was used to remove the ocular artifacts).
c. Re-referencing to averaged mastoid electrodes, averaged ear-lobe electrodes, or common reference.
d. Band pass filtering at 0.1-30 Hz.
e. Segmentation into 2200 ms segments starting 200 ms before triangle onset as baseline.
f. Baseline correction.
g. Artifact rejection (typically the maximum and minimum voltage was set at ± 70 μV and any segments exceeding this criteria are removed).
h. Average the segments to yield ERP wave.
i. Peak detection: N100 referring to the negative maximum peak within 150-250 ms after trial onset; N2 referring to as the negative maximum peak within 500-700 ms after trial onset, i.e., 200-400 ms after the Go/NoGo signal; P3 referring to the maximum positive peak with 600-900 ms, i.e., 300-600 ms after the Go/NoGo signal. Detected peaks are always visually inspected.
j. Exporting the peak voltage or window average voltage. N2-P3 amplitude is calculated by subtracting the amplitude of N2 from the amplitude of P3.

3.6 Frontal Alpha Asymmetry

Frontal alpha asymmetry was calculated between frontal electrodes F3 and F4 as suggested (Davidson, 1995). The typical procedures was:

a. Down-sampling to 250 Hz.
b. Ocular correction.
c. Re-referencing to electrode Cz.
d. Filtering at 3-30 Hz.
e. Segmentation into 2000 ms segments starting from the onset of each trial, i.e., the triangle.
f. Artifact rejection where any segment with amplitude exceeding ± 80 μV was removed.
g. Fast Fourier transformation (FFT) to calculate the power spectrum ($\mu V^2/Hz$).
h. Averaging the power of all segments.
i. Exporting the alpha (8-13 Hz) power (μV^2).
j. Log-transformation of the alpha power of EEG electrodes F3 and F4.
k. Making difference by subtracting the power at F4 by the power at F3.

3.7 Statistics

Repeated measure analysis of variances (ANOVA) was used in the analysis of RTs, ERP amplitudes, and frontal alpha asymmetry. In the analysis of RTs, only RTs with correct response and longer than 150 ms were analyzed. Due to the requirement of normal distribution, RTs were log-transformed. The used factors for repeated measures ANOVA included Stimulation/Extraocular light statuses (ON vs. OFF) and Emotion (emotional vs. neutral). In the analysis of ERPs, peak amplitudes of a number of regional electrodes, were analyzed. For example, in the analysis of P3 amplitudes in article IV, P3 amplitudes of nine centro-parietal electrodes were exported, averaged and analyzed. ERP data are usually normally distributed. Compared to the analysis of RTs, response type (Go vs. NoGo) was used as an additional factor.

For RTs and ERPs in smaller group subjects in article II, non-parametric statistical method, i.e., the Wilconxon signed rank test, was used to analyze the impact of emotional valance under different neuromodulation conditions. Symmetry of differences was guaranteed with Miao, Gel, and Gastwirth symmetry test. Asymptotic K-sample Fisher-Pitman permutation test was used to compare the impact of different emotional valence.

Behavioral errors are on a categorical scale and we used generalized binary logistic regression to analyze response accuracy. The Executive-RT test has two types of

responses, Go or NoGo cases, and generates three types of errors. In Go cases, incorrect button presses and misses were analyzed. Outcomes in the Go cases were dichotomized into either errors (e.g., misses in Go cases) or others (incorrect and correct button presses in Go cases). Similarly for incorrect button presses, errors represents incorrect button presses and others include both misses and correct button presses. In NoGo cases, any button presses lead to commission errors. Thus, outcomes were either errors (i.e., commission errors) or others (no button press in NoGo cases). Separate models are built for each error type, where factors (or predictors) are Stimulation, Emotion and Subject as a randomized predictor.

All statistics were done using R statistics (the R-foundation for Statistical Computing, version 3.1.1.). Repeated ANOVA was done using ez package (Lawrence, 2013). Logistic regression analysis was done using with lme4 package (version 1.1-10) (Bates et al., 2014).

4 Summary of the Results

We investigated the immediate effects of neuromodulation on human cognitive and affective functions using a within subject design. Specifically, each subject is the control for him/herself at different neuromodulation status. We compared the immediate behavioral and brain electrophysiological difference between conditions when neuromodulation was on and when it was off. Both behavioral and electrophysiological findings are summarized below.

4.1 Summary of Findings in Article I & Article II

Patients with ANT-DBS are heterogeneous with some of them performing poorly in the Executive-RT test, some having unanalyzable ERPs and some with no proper ANT locations. In article I, analysis of behavioral data was done for both subgroup of patients with good performance (n = 7) and the whole group (n = 11). In article II, only patients having good performance, proper ANT locations and analyzable ERPs (n =6) were included in the analysis. Also, in these two articles, the stimulation statuses were handled differently. In article I, conditions when stimulation was OFF at ANT and OFF at the control location (i.e., the OA) were treated differently considering the location-related carry-over effect. Thus, there were four neuromodulation-related conditions: ANT ON, ANT OFF, control location ON and control location OFF. In article II, ANT OFF and control location OFF were combined and there were three conditions: ANT ON, control location ON, and OFF.

While ANT-DBS was ON, patients had increased emotional reactivity as reflected in slowed RTs. In article II, when stimulation was ON at ANT, slowed RT was found with the presence of threat-related distractors compared to neutral distractors, $z = -2.2014$, $p = 0.03$. Stimulating a thalamic control location a few millimeters deeper toward the medial thalamus did not give similar effects, Fig. 9.

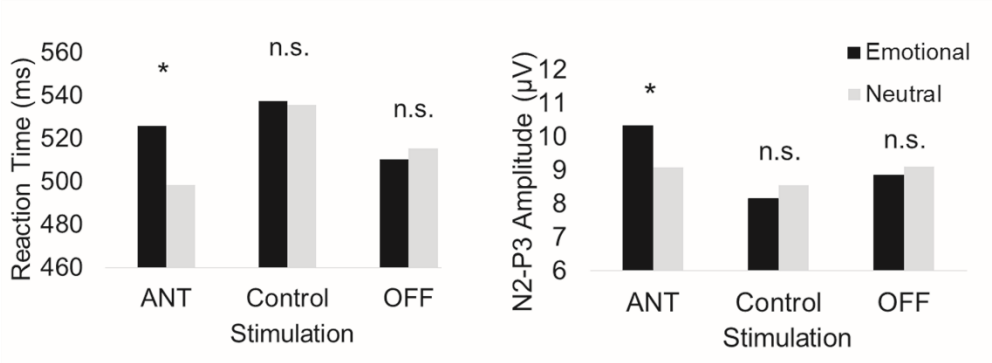

Figure 9. ANT-DBS leads to increased attentional allocation to threat-related distractors, seen as increased RTs and enhanced N2-P3 amplitude in context of emotional stimuli (Sun et al., 2015). The main effect of Emotion was marked. * refers to that 0.01< p < 0.05.

Concurrently, emotional distractors lead to increased centro-parietal N2-P3 amplitude when stimulation was ON at ANT, z = -2.2014, p = 0.03, but not during control location ON or OFF conditions. N2-P3 peak-to-peak amplitude are shown in Fig. 10.

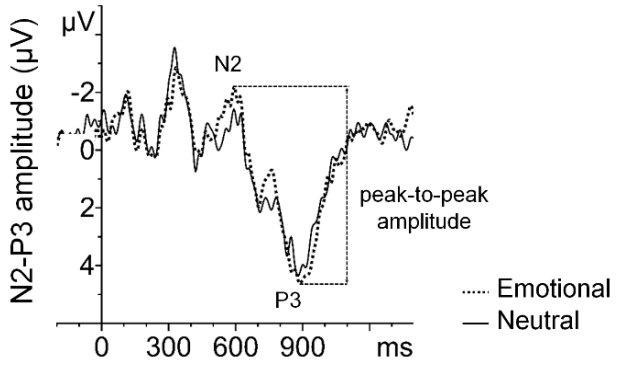

Figure 10. Illustration of N2-P3 measure. Greater N2-P3 amplitude in context of emotional distractors due to ANT-DBS.

In article I when the whole group of patients were included in the analysis, stimulating ANT led to increased amount of commission errors [ANT ON (10.32% ± 9.16%), ANT OFF (7.17% ± 8.10%); F (1, 10) = 5.44, p = 0.05]. No changes of commission errors were found at the control location, F (1, 10) = 0.15, p = 0.71. Furthermore, when only the good performers were involved in the analysis, stimulation ON at ANT and control location led to increased amount of misses [ON (3.79% ± 3.03%), OFF (0.93% ± 0.99%); F(1, 6) = 7.04, p = 0.04]. However, these findings were not found in article II with smaller group of subjects.

4.2 Summary of Findings in Article III

When the cyclic VNS was ON, improved working memory performance and enhanced visual attention was found compared to VNS OFF. Incorrect button presses, in response to direction of the previously presented triangles, were less when VNS was on compared to when it was off, OR = 0.63 (95% CI 0.47-0.85), Fig. 11. Concurrently, parieto-occipital N1 amplitude was increased when VNS was ON indicating enhanced visual attention, F (1, 15) = 10.17, p = 0.006.

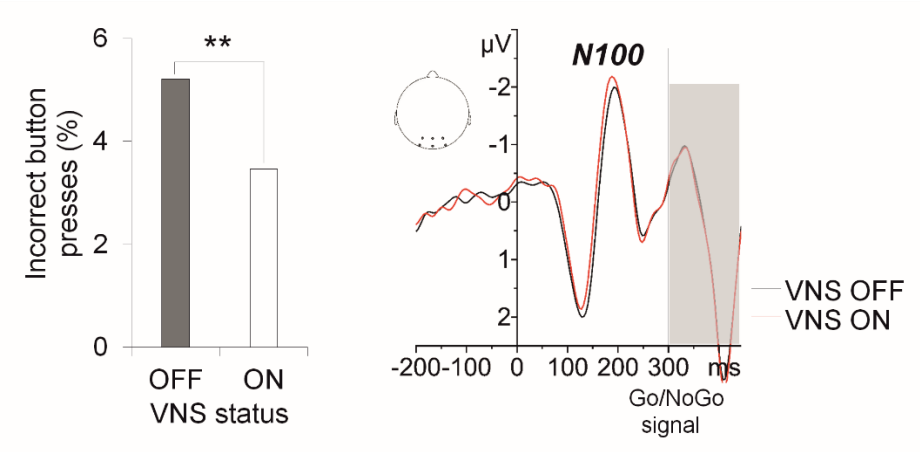

Figure 11. VNS ON led to reduced amount of incorrect button presses (left) and greater parieto-occipital N1 amplitude (right), suggesting improved working memory performance and enhanced attention.

Analysis of RTs resulted in an interaction effect between Stimulation and Emotion, F (1, 16) = 5.15, p = 0.04. In the presence of threat-related distractors the RTs were longer when VNS was on compared to when it was off, F (1, 16) = 8.23, p = 0.01, Fig. 12. This effect was not found with neutral distractors, F (1, 16) = 0.48, p = 0.50. The same interaction between Stimulation and Emotion was found in the analysis of frontal alpha asymmetry, F (1, 16) = 7.13, p = 0.02. Increased RTs also went along with enhanced right-sided frontal alpha asymmetry, F (1, 16) = 11.79, p = 0.003. This phenomenon did not exist when there were neutral distractors. F (1, 16) = 0.54, p = 0.47.

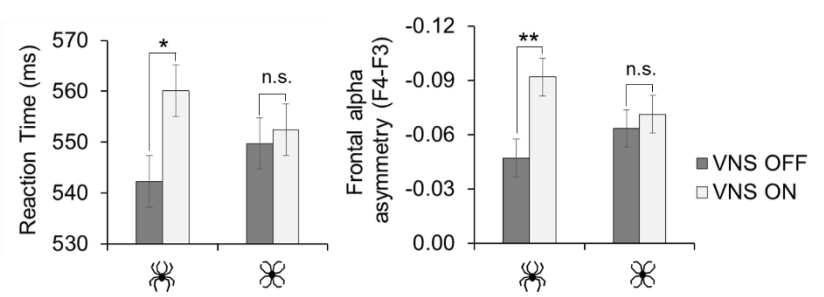

Figure 12. With the presence of emotionally negative distractor, VNS ON led to increased RTs and frontal alpha asymmetry. No similar phenomenon was found with neutral distractors.

4.3 Summary of Findings in Article IV.

We compared the behavioral performance and brain electrophysiology in situations when extraocular light was delivered via the ear canals and when it was not. No behavioral modulation was found. However, light modulated parietal P300 amplitude, indicating that human brain reacts to extraocular light. We also showed in a cadaver that bright light is capable of penetrating through the human skull.

Analysis of the parietal P300 amplitude resulted in an interaction effect between Extraocular light and Emotion, $F(1, 17) = 25.48$, $p = 0.0001$. When there was no extraocular light (OFF condition), emotional distractors led to reduced parietal P300 amplitude compared to neutral distractors, $F(1, 17) = 10.83$, $p = 0.004$, Fig. 13. When extraocular light was ON, no similar phenomenon was found, $F(1, 17) = 2.48$, $p = 0.13$. This finding is innovatory and future studies are needed for validation.

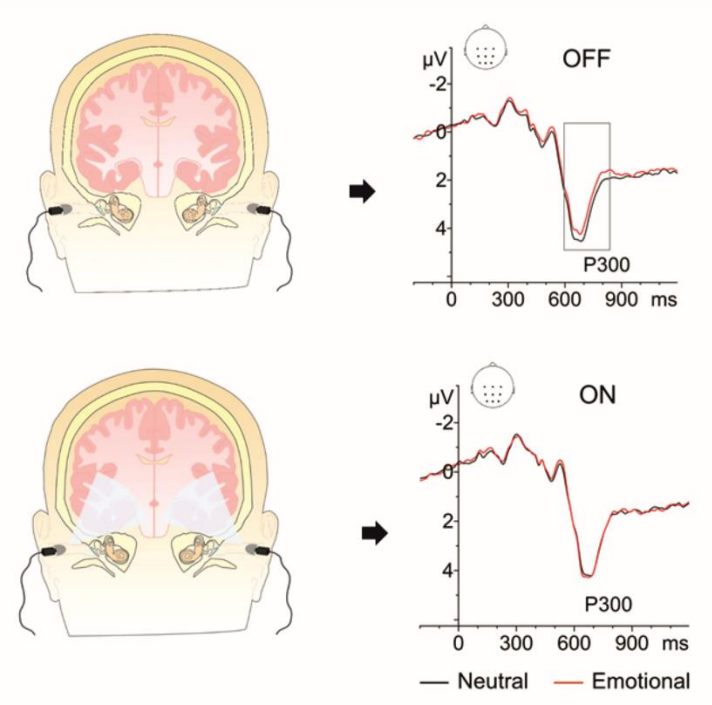

Figure 13. When no light was given, emotional distractors reduced the parietal P300 amplitude compared to neutral distractors. When bright light was delivered, this effect disappeared (Sun et al., 2016).

4.4 Behavioral Comparison between Groups of Subjects

Comparison of behavioral findings including RTs and incorrect button presses in all groups of subjects was done. Patients with ANT-DBS treatment includes seven subjects with proper ANT locations and good performance. Patients with VNS treatment involved 17 subjects with good performance. Included healthy subjects for study using extraocular light neuromodulation are the same with those in article IV.

Neuromodulation techniques, ANT-DBS and VNS, altered emotional responses and affected behavioral performance. This was illustrated by the interaction effects between Emotion and Stimulation statuses [ANT-DBS, $F(1, 6) = 12.37$, $p = 0.01$; VNS, $F(1, 16) = 5.15$, $p = 0.04$)], Fig. 14. Extraocular light delivered via the ear canals had no effect on behavior.

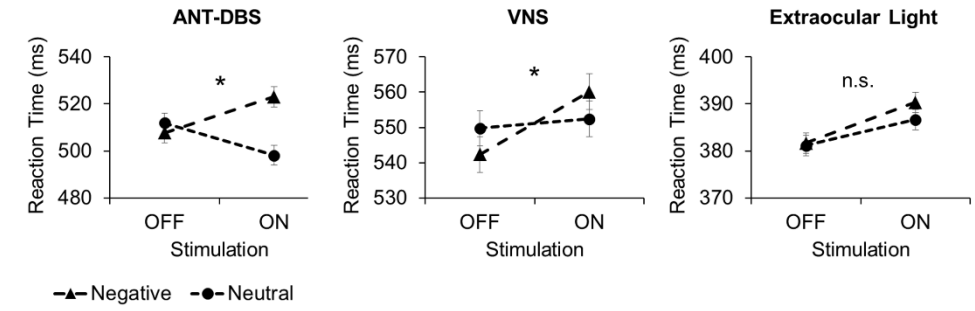

Figure 14. Analysis of reaction times for all groups of subjects using ez ANOVA. Interaction effect between neuromodulation status and emotion are illustrated. n.s. = no significance.

VNS had a main effect on the rate of incorrect button presses (incorrects). VNS ON reduced the amount of this type of errors compared to VNS OFF, OR = 0.63 (95% CI 0.47-0.85), Fig. 15. ANT-DBS and extraocular light did not affect this type of errors. No effects of emotion were found.

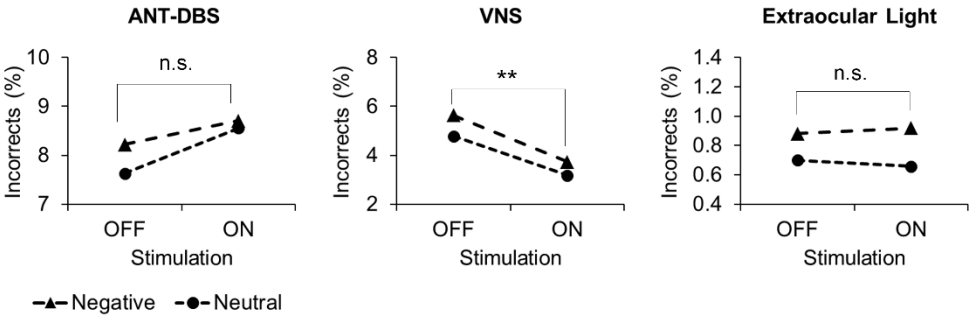

Figure 15. Analysis of incorrect button presses (Incorrects) using logistic regression. n.s. = no significance. VNS decreased the number of incorrects suggesting improved working memory performance. No significance was found for other error types.

In article I, ANT-DBS was associated with increased commission errors only when the whole group was included for analysis. Also, effect of ANT-DBS on misses was found when the subgroup of good performers were analyzed. Since these findings were not confirmed in article II, and VNS and extraocular light had no effects on these errors, no comparison was done between groups.

5 Discussion

Novel neuromodulation techniques provide unique opportunities to study the brain circuits and functioning in living humans. Clinically applied ANT-DBS allowed us to illustrate the critical role of ANT in human emotion-attention interaction. We are the first to provide direct behavioral and electrophysiological evidence for ANT's role in emotional control in humans, while previously ANT's role in human emotion was mainly inferred from its connections with other limbic structure. The evidence for VNS improving working memory performance and enhancing visual attention with clinically relevant stimulation parameters is novel and significant, with earlier reports on VNS's effects on cognition being controversial and limited to theoretical interest. The beneficial effects of VNS are in line with subjectively reported cognitive improvement and they also shed light on the important role of peripheral inputs for human cognitive and affective functions. In addition, we found that extraocular light delivered via the ear canals alters emotion related brain potentials pointing to possible extraocular light sensitivity of human brain and calling for further investigation.

Combination of cognitive tests with tailored neuromodulation protocols turned out to be a sensitive method to uncover the immediate effects of neuromodulation approaches on human cognitive and affective functions. One key advantage of this method is the use of within subject design to measure possible immediate effect. Specifically, each subject is the control for him/herself. We compared the immediate behavioral and brain's electrophysiological differences between situations when neuromodulation was on and when it was off. In this way, we were able to avoid confounding factors such as medication, changes in social dynamics and natural course of diseases leaving any detectable difference directly attributed by neuromodulation.

5.1 ANT-DBS and Human Executive Functions

High frequency electrical stimulation generates a reversible "lesion" effect on ANT, providing a unique opportunity to study its role in human cognitive and affective

functions. Taking advantage of the clinically applied ANT-DBS for referactory epilepsy, we found increased attention allocation to threat when the function of ANT was temporarily disrupted, as seen in increased RTs and event-related brain potentials due to threat-related distractors (Hartikainen et al., 2014; Sun et al., 2015). The settings of ANT-DBS were blinded to all subjects. Electrical stimulation at a control location just a few millimeters inferior into the thalamus did not give similar effects highlighting the specific role of ANT and its networks in emotion-attention interaction.

The ANT is a key node of the limbic system with three subnuclei, i.e., the anteroventral, anterodorsal and anteromedial nuclei (Jones, 2007). These subnuclei have distinct connectivity with subcortical brain regions including the hippocampus, retrosplenial cortex and mammillary bodies. ANT, particularly the anteromedial nuclei, also holds extensive reciprocal connection with the OFC and the ACC (Xiao and Barbas, 2002a, b). Hence, ANT is an important node bridging these subcortical regions with the prefrontal cortex. It is therefore proposed to have potential role in human executive functions and emotional control (Child and Benarroch, 2013). ANT-DBS, by introducing a reversible lesion effect at ANT, provides a unique chance to study the role of ANT in human emotion, attention and cognition.

ANT-DBS, using high frequency electrical stimulation to generate a reversible lesion effects at ANT, bears advantages over brain lesion studies. Firstly, large number of patients with specified lesion at the ANT are not available. Secondly, traditional brain lesion studies do not directly demonstrate the function of the lesioned brain area, but instead illustrate the functional changes of the brain after lesion. Further, these brain lesion studies are usually conducted long time after the lesion. Brain's functional reorganization allows other brain areas to at least partially compensate the function of the lesioned brain area perplexing the reported cognitive and affective changes after lesion. In contrast, ANT-DBS allows us to study the function of the brain with and without intact ANT functioning in a number of patients with specified "lesion" at ANT. Also, the temporal "lesion" effect better controls the influence of chronic plastic changes which take place after permanent lesion, although chronic DBS might also induce neuroplasticity and alter normal brain function. Likewise, epilepsy disorder may alter cognitive and affective brain functions warranting caution when making conclusions from this population about normal brain functions.

Alternating ANT-DBS ON and OFF while patients perform the Executive-RT test allows to uncover the role of ANT in human executive functions. Traditional neuropsychological tests are not suitable for detecting the immediate effects of

ANT-DBS, not only in respect to sensitivity but also due to the lack of repeatability within short periods. The Executive-RT test has been shown sensitive in detecting subtle cognitive and affective modulation due to mild brain injury (Hartikainen et al., 2010b; Hartikainen et al., 2012a; Mäki-Marttunen et al., 2015). Patients having undergone ANT-DBS for epilepsy performed this test while the electrical stimulation was continuously on and when it was off. This allows to control confounding factors (e.g., medication and natural course of epilepsy) and to uncover the direct and immediate effect of ANT-DBS on human cognition and emotion. Following this approach, we found that when ANT-DBS was on, patients paid more attention to threat related distractors with increased RTs and increased centro-parietal N2-P3 amplitude indicating increased attention allocation to threat (Hartikainen et al., 2014; Sun et al., 2015).

These findings may come from weakened top-down emotional control (Fig. 16). The brain's executive functions allow us to focus on the goal of the task while avoiding being distracted by task-irrelevant stimuli. Particularly, the prefrontal lobe integrates information from all other brain subregions and execute top-down control (Alvarez and Emory, 2006). For instance, the OFC is involved in emotional control and impaired OFC may lead to imbalanced attention allocation between the target and emotional stimuli (Hartikainen et al., 2012a). Given the direct connection between ANT and OFC (Xiao and Barbas, 2002a), electrical stimulation at ANT might affect the function of the OFC leading to deteriorated top-down emotional control and increased attention allocation to threat. Also, ANT reciprocally connects with the ACC (Xiao and Barbas, 2002a; Child and Benarroch, 2013) which has been involved in various cognitive and affective functions (Bush et al., 2000). In a proposed model by Shenhav et al, ACC is thought to be a key node for evaluating all sensory information and provide these information to the prefrontal cortex to execute cognitive control (Shenhav et al., 2013). Thus, it is also possible that ANT-DBS led to biased or noisy inputs into ACC and resulted in executive dysfunction.

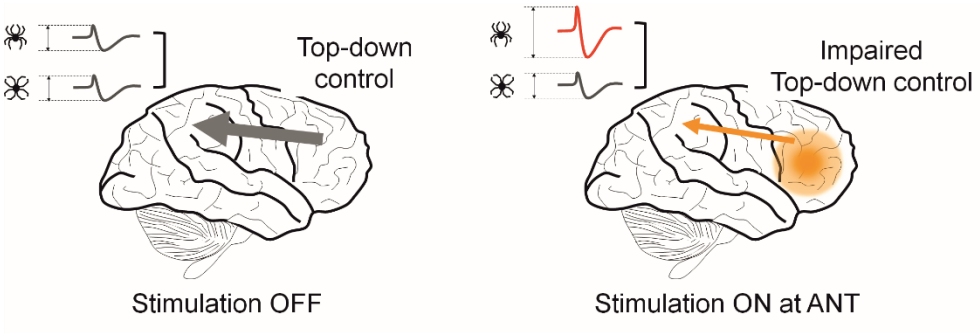

Figure 16. Schematic presentation of the ERP changes due to ANT-DBS. ANT-DBS may impair the brain top-down control function leading increased attention allocation to threat as shown by ERP changes at the centro-parietal region.

ANT-DBS impairing executive functions may be further evidenced by the impaired response inhibition, as seen in increased commission errors when all twelve patients were involved in the study (Hartikainen et al., 2014). Since subjects are supposed to withhold from pressing any button, increased commission errors indicated impaired response inhibition. Response inhibition, although via distinct cognitive strategies from emotional suppression, is also related to brain's inhibitory control – an important element of the human executive functions. A different inclusion criteria, where patients with unanalyzable ERPs, improperly defined ANT locations and poor behavioral performance were excluded, generating a subgroup of six subjects (Sun et al., 2015), however, did not give the similar finding in commission errors making the effect of ANT-DBS on response inhibition ambiguous. The discrepancy might root from reduced statistical power in a smaller group of subjects ($n = 6$ vs. $n = 12$). Meanwhile, it is also possible that increased commission errors were mainly conveyed by patients whose cognitive performance was poor. In contrast, electrical stimulation at ANT leading to increased emotional reactivity has been validated in both article I and article II regardless of the sample size and the inclusion criteria of subjects.

In addition to behavioral findings, we also used the centro-parietal N2-P3 amplitude to index attentional resource allocation. ERP studies in patients with severe epilepsy are challenging due to the frequent epileptiformic activity and slow wave shifts in their EEG. In comparison to traditional single peak analysis, the N2-P3 peak-to-peak amplitude measure enables better control for the interference of slow wave fluctuations. Increased N2-P3 peak-to-peak amplitude associated with

increased RTs indicate increased attention allocation to threat-related distractors due to ANT-DBS.

Increased attention allocation to negative stimuli is a hallmark of emotional disorders such as anxiety and depression (Kindt and Van Den Hout, 2001). Our finding that ANT-DBS increased attention allocation to threat, as seen in both behavioral and electrophysiological evidence, might explain the self-reported increase in depression related symptoms due to clinically used ANT-DBS for epilepsy (Fisher et al., 2010; Salanova et al., 2015). However, we used continuous electrical stimulation when ANT-DBS was on and no stimulation when it was off, which is different from the clinically used intermittent mode, e.g., one minute on and five minute off. Therefore, the results from our ANT-DBS studies are not directly applicable in to clinical setting. Whether the increased attention allocation to threat is correlated with those self-reported depression related symptoms calls for further investigation. Furthermore, direct link between current findings and clinical depression related symptoms may be complicated (Mathews and Mackintosh, 1998). Given that patients with chronic epilepsy have been reported to have declined emotional response to fearful faces (Meletti et al., 2009), whether the current finding that ANT-DBS increased attentional allocation to threat indicates impaired or normalized emotional reactivity needs to be investigated.

In conclusion, taking advantage of clinically applied ANT-DBS, we demonstrated the important role of ANT in human emotion-attention interaction. Our finding that high frequency electrical stimulation at ANT increased attention allocation to threat calls for careful consideration of affective side effects during the medical treatment for epilepsy using ANT-DBS. Our study also provided potential behavioral and electrophysiological biomarkers for evaluating these affective effects, although further validation of these biomarkers is needed.

5.2 VNS, Human Cognition and Emotion

We compared the cognitive performance and brain electrophysiology when VNS was administrated and when it was not. We found that VNS improved accuracy of working memory performance as seen in reduced amount of incorrect button presses. This cognitive improvement went along with increased parieto-occipital N1 amplitude suggesting improved visual attention. We found that VNS increased RTs and frontal alpha asymmetry in the presence of emotionally threating distractors indicating enhanced vigilance to threat.

Although VNS is clinically used for treating refractory epilepsy and depression, its exact mechanism of action remains unclear. VNS modulates the level of brain neurotransmitters such as the norepinephrine (NE) (Roosevelt et al., 2006; Follesa et al., 2007) which may play crucial role in the modulated human cognition and emotion (Vonck et al., 2014; Grimonprez et al., 2015a; Grimonprez et al., 2015b). Anatomically, the VNS innervates the nucleus tractus solitaries (Kalia and Sullivan, 1982) which is further connected to the locus coeruleus (Aston-Jones et al., 1991; Van Bockstaele et al., 1999) the principal site for the brain's synthesis of NE (Aston-Jones and Cohen, 2005). NE holds widespread projections to the limbic area and cortical regions which are critical for working memory, memory and other cognitive functions. It is reported that increased level of NE enhances brain's sensory responses (Foote et al., 1975; Bouret and Sara, 2002), promotes signal transmission between neurons (Hopkins and Johnston, 1984) and improves cognitive functions (Ramos and Arnsten, 2007) in both humans and primates. Therefore, functions of the neural circuits behind working memory may improve, as we found using VNS, due to increased NE.

VNS improved working memory performance accompanied by increased parieto-occipital N1 amplitudes. Although our cognitive task is not a specific working memory test, the requirement to hold the direction of the triangle in memory and to press the corresponding button at least partially reflects the working memory functions. Meanwhile, the visual N1 amplitude at the parieto-occipital brain region has been linked with attention in the way that increased N1 amplitude indexes enhanced visual attention (Mangun and Hillyard, 1991; Luck and Ford, 1998). Working memory and attention are tightly intertwined with attention providing the basis for registering information into working memory (Awh et al., 2006), the improved working memory performance in the Executive-RT test is possibly due to enhanced early visual attention. However, considering that the task only posed low demands on working memory, more specified working memory tests may be used in the future to validate these conclusions.

In addition to the improvement in working memory performance, we also found that VNS immediately increased vigilance to threat as seen in increased RTs with the presence of negative distractors. Along with the increased RTs, we also found enhanced task-related frontal alpha asymmetry indicating increased right hemispheric activity. Increased vigilance to threat-related stimuli and right hemispheric activity is sometimes linked with predisposition toward psychopathology (Kindt and Van Den Hout, 2001; Grimshaw et al., 2014). However, these findings seem to be paradoxical with the application of VNS for treating

refractory depression and the generally reported improvement of depressive symptoms after treatment (O'Reardon et al., 2006; Vonck et al., 2014; Grimonprez et al., 2015b). We have proposal for this conflict. Firstly, considering the anxiolytic and anxiogenic effects of NE which has a time course dependency (Goddard et al., 2010), temporally increased vigilance, if induced by increased NE, may eventually lead to a long-term beneficial effects. Secondly, the increased NE due to VNS might lead to enhanced signal-to-noise ratio and visual perception of threat-related stimuli (Sara, 2009) leading to increased vigilance, which virtually has no psychopathological indication. On the other hand, some patients with severe epilepsy, e.g., those with TLE, are sometimes characterized with emotional dysfunction such as impaired emotional response to fearful facial expression (Meletti et al., 2009). It is also possible that VNS brings beneficial affective effects with restored emotional reactivity. Furthermore, while increased resting state frontal alpha asymmetry is often linked with predisposition toward psychopathology (Davidson, 1995), whether similar changes during a cognitive task has similar link to psychopathology remains exploratory. Thus, since numerous factors can cause immediate increase of vigilance, a comparison between immediate effect and long term outcomes better addresses the impact of VNS on mood.

Thus, we have found that clinically used VNS has immediate improvement on human working memory performance along with electrophysiological evidence for enhanced visual attention. Further, VNS also increases vigilance to threat as seen in increased RTs and frontal alpha asymmetry. Our finding that VNS improves working memory performance goes in line with those generally reported mood and cognitive improvements (Vonck et al., 2014; Grimonprez et al., 2015b). Uncovering VNS' immediate effects on human cognition and emotion by comparing behavior and brain electrophysiology between stimulation on and off has significance clinical impact and methodological merits.

Further, our study also provides supportive evidence for studying the potential of VNS as a medical treatment for other cognitive and attention related disorders. For instance, VNS enhancing human attention and improving working memory might provide additional opportunities for neuroprosthetics. VNS pairing with sensory events can generate long-lasting and highly specific plasticity and it is thought a promising method in treating tinnitus (Engineer et al., 2011; De Ridder et al., 2014). Tinnitus is characterized by hearing without auditory stimulation and it is often treatment resistant. VNS combined with sustained auditory stimulation at certain frequency has been found to reduce tinnitus symptoms at least in some patients (De Ridder et al., 2014). One potential explanation is that VNS elevates the

levels of brain chemicals that eases the sensory stimuli to wire cortical tuning frequency and leads to enhanced sensory processing (Hays et al., 2013; Engineer et al., 2015). Likewise, VNS pairing with specified psychotherapeutic training, e.g., activities to promote concentration, might promote the modulation of human brain networks to restore attentional deficits. Besides, the noninvasive approaches of VNS may further propagate its application as a potential neuroprosthetic treatment for attentional and cognitive dysfunctions, calling for future studies.

5.3 Extraocular Light and the Brain Responses

We found that transcranial extraocular light modulated human brain processing of emotional stimuli as indicated by modified brain potentials, i.e., the parietal P300 amplitude. We also showed in a cadaver that visible blue-enriched light can penetrate through the human skull via the auditory canals. Our study suggested the sensitivity of human brain to extraocular light, calling for future study on the potential mechanisms.

Deep brain photoreceptors in the hypothalamic and septal regions of bird's brains respond to transcranial extraocular light and modulate seasonal behaviors (Foster et al., 1985; Nakane et al., 2010). Although photosensitive proteins such as Opsin 3 and Opsin 5 are also present in the human brain (Tarttelin et al., 2003), whether mammalian brains possess similar light sensitivity to transcranial light is unknown. Studies showing long-term effects of transcranial extraocular light on humans have limitations including conflict of interest or the lack of proper controls (Timonen et al., 2012; Jurvelin et al., 2014; Tulppo et al., 2014). Further, if any, the short-term effects of this light may be too subtle to detect using behavioral tests (Bromundt et al., 2014) further supporting the general belief that mammals may lack similar deep brain photosensitivity.

Since similar approaches as used in the studies of birds' brains are not applicable in the study of humans, we used ERPs which are sensitive tools to measure possible neuromodulation effects due to transcranial light. We found that when no extraocular light was given, emotional distractors led to reduced parietal P300 amplitude. This might be due to increased brain's top-down control triggered by emotional distractors, with greater top-down control leading to reduced attentional allocation to targets. Similar phenomenon has been found during divided attention tasks where distracting task results in smaller parietal P300 amplitude and poorer recognition memory (Curran, 2004). Also, increased task load is reported to reduce

attentional allocation to target as reflected in smaller parietal P300 amplitude in working memory tasks (Kok, 2001), supporting this proposal. In contrast, when extraocular light was delivered emotion-related changes of P300 amplitude disappeared.

Blue-enrich transcranial light delivered via the auditory canals is capable of penetrating the human skull and modulate human brain potentials related to emotional processing. However, the exact mechanism of this process is still unknown. Although we used blue-enriched light in the study, whether the major contributor of these effects is the blue light itself directly affecting brain function remains exploratory. The LED light generator potentially produces heat which might warm up the ear canals potentially contributing to these effects. The heating effect, however, was not considered to be significant since the effect of subtle heating is typically low (Wade et al., 1988; Starck et al., 2012). In addition, previous studies by Starck et al using functional magnetic resonance imaging demonstrated that at resting state light delivered via the ear canals lights up the backside of retina (Starck and Nissil, 2012). Given the brain is floating in cerebrospinal fluid it is not impossible that the scattered light can reach the backside of retina and affects brain functioning similarly as ocular light. Thus, the exact mechanism of action of extraocular light on human and mammalian brains call for future studies.

We have demonstrated that the human brain reacts to extraocular light delivered via the ear canals. The study was properly controlled between light delivery ON and OFF allowing for immediate comparison of its effects on human brain functioning. This study was also conducted as a pilot study on healthy subjects for studying the immediate effects of neuromodulation on emotional and cognitive functions. The study was not designed to discover the mechanism of potential deep brain photosensitivity, e.g., possible existence of deep brain photoreceptors in the human brain, nor to test whether the Bright Light Ear Headset relieves human affective disorders. Therefore, the subtle effect of extraocular light on human brain potentials is by no means indication of usefulness of the Bright Light Ear Headset for treating seasonal affective disorders.

5.4 ERPs as a Tool to Study Neuromodulation

ERPs are convenient tools in studying human cognitive processes, especially owing to their being a continuous measure of cognitive processing and possessing high temporal resolution. They provide online information of human brain physiology

and its alteration due to neuromodulation. Also, ERPs are sensitive tools for uncovering online information processing of brain events with no behavioral outcomes (Luck., 2005; Boly et al., 2011; Kouider et al., 2013). However, beyond these advantages, using ERPs to study the cognitive and affective effect of neuromodulation also has challenges.

Firstly, patients with epilepsy sometimes have unanalyzable ERPs. As in article II, several subjects were excluded due to frequent epileptiformic discharges leading to unrecognizable ERPs. Also, slow waves shifts challenge the traditionally used single-peak analysis. Secondly, electrical brain stimulation may contaminate the EEG signal. In our studies using ANT-DBS, bipolar electrical stimulation was used partially due to monopolar DBS contaminating the ERP signal.

Concerning challenges due to slow wave shifts, we used the N2-P3 peak-to-peak amplitude as an index of attentional resources instead of single-peak analysis for patients with ANT-DBS. The peak-to-peak measure allows us to better constrain the influence of slow wave shifts. We found that N2-P3 peak-to-peak amplitude may be a potential biomarker for the modulated emotion-attention interaction due to deep brain electrical stimulation.

5.5 Potential Behavioral and Electrophysiological Biomarkers

Both ANT-DBS and VNS modulated emotion-attention interaction as indicated in altered RTs and ERPs during the Executive-RT test. These objective behavioral and electrophysiological measures may benefit the clinical treatment in respect of better controlled adverse cognitive and affective effects and provide candidate biomarkers for this. Take ANT-DBS for example, considering the lack of immediate motor response (like the stimulation of subthalamic nuclei for treating Parkinson's disease) and no immediate measure for mild cognitive and affective changes, post-operative optimization for efficient seizure control takes a long time. Successful seizure reduction has been linked with a more superior and anterior part the ANT (Lehtimäki et al., 2016), highlighting the importance of detailed anatomical and functional knowledge of the exact location of the stimulated contact in ANT-DBS (Möttönen et al., 2015; Möttönen et al., 2016). Even the most developed neuroimaging technique, however, does not allow for exact localization during the implantation of IPG electrodes. To that end, biomarkers giving additional information to brain imaging methods and helping determine appropriate electrode locations are beneficial. In our current study, the seizure-control-efficient location,

the ANT, was linked with increased attention allocation to threat. Stimulating control locations even a few millimeters away toward the medial thalamus did not give similar effects (Hartikainen et al., 2014; Sun et al., 2015). Therefore, the specific modulatory effect of ANT stimulation, i.e., only stimulation at ANT lead to altered emotion-attention interaction, can help to tune post-operatively the IPG electrode locations, e.g. by choosing active contacts inside or closest to ANT.

Optimized medical treatment should have minimal affective and cognitive side effects, calling for cognition and emotion-related biomarkers. However, before possible clinical application of these biomarkers, a few concerns should be addressed. First, how are the immediate effects linked with long-term effects, or there any links? For example, can the increased attention allocation to threat predict predisposition toward depression-related symptoms due to ANT-DBS? Second, if this link exists, is it specific for the type of neuromodulation? For instance, if the link that immediate increase of attention allocation to threat predicts long-term adverse affective effects exists, is it specific to ANT-DBS? Is this link for VNS in an inversed way? These questions may be answered along with the increasing understanding of the specific mechanisms of neuromodulation. After addressing these concerns, potential biomarkers should be validated using larger samples before clinical applications.

5.6 Scientific, Clinical and Societal Impacts

Emotional and cognitive health is important for one's quality of life. Nevertheless, mental dysfunctions tend to be neglected unlike motor or sensory deficits. Traditional neuropsychological methods are not sensitive or capable of detecting subtle emotional dysregulations and cognitive deficits. These subtle dysfunctions, however, may hinder us from adapting to modern day information society where even a simple task might demand good knowledge of modern technological tools such as computers and other smart machines. Those with dysregulated emotion and behavior may be easily challenged by handling problems caused by our busy life. Cognitive and affective dysfunctions might eventually cause withdrawal in social relationships and failure to maintain employment. Therefore, the personal and societal costs of emotional and cognitive dysfunctions might be profound.

Neuromodulation may lead to changes of emotional and cognitive functions. In the current thesis, we found that ANT-DBS for controlling seizure frequency also led to increased attention allocation to threat (Hartikainen et al., 2014; Sun et al.,

2015). Previously, patients with ANT-DBS have been reported to have subjective memory related problems and depression related symptoms (Fisher et al., 2010). These emotional and cognitive changes should not be regarded only as less important side effects, but instead highlighted in order for optimized medical treatment. Detection and proper control of emotional and cognitive changes, as are the aims of the current thesis, bears both clinical and societal impacts.

In addition, neuromodulation treatments also provide unique chances to study neural circuits underlying human cognition and emotion. Therefore, the current thesis also holds neuroscientific significance. For example, ANT-DBS as used for treating refractory epilepsy provides a unique opportunity to study the brain circuits involving ANT and their roles in human emotion. Uncovering the potential extraocular photosensitivity of human brain may add novel insights to photobiology.

5.7 Future Prospectives

Our studies have uncovered the immediate effect of neuromodulation techniques on human affective and cognitive functions. More specific tests are needed to delve into different aspects of executive functions. For instance, specific response inhibition tests may be applied to investigate the effect of ANT-DBS. Specific working memory tests can be used for in-depth investigation of the effect of VNS.

Further, we found potential biomarkers for objectively measuring the cognitive and affective effects due to neuromodulation, including reaction time changes, N2-P3 peak-to-peak amplitude and frontal alpha asymmetry. Due to the small size of sample, however, large scale test is needed to further investigate whether the affective changes relate to depression.

Finally, our finding that human brain reacts to transcranial extraocular light requires further confirmation, e.g. studies in anophthalmic individuals. Also, the exact mechanism is remains exploratory. Whether the human brain possess deep brain photoreceptors needs to be further investigated.

6 Conclusion

a. Continuous electrical stimulation at ANT increases attention allocation to threat calling for careful consideration of affective side effects of ANT-DBS treatment.
b. ANT is involved in emotion-attention interaction as evidenced by direct behavioral and brain electrophysiological evidence from humans.
c. VNS improves working memory performance and enhances visual attention providing novel support for its benefits on cognition in treatment of patients with epilepsy. VNS has immediate effects on affective and cognitive functions as indicated by behavioral and brain responses to emotional threat-related stimuli.
d. Electrophysiological but not behavioral changes suggest that human brain reacts to transcranial extraocular light. However, this result calls for further validation.
e. The study identifies potential biomarkers for the altered emotion-attention interaction due to neuromodulation, including emotional interference of RTs and modulation of centro-parietal N2-P3 peak-to-peak amplitude, and the frontal alpha asymmetry.

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

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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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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 respective 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.

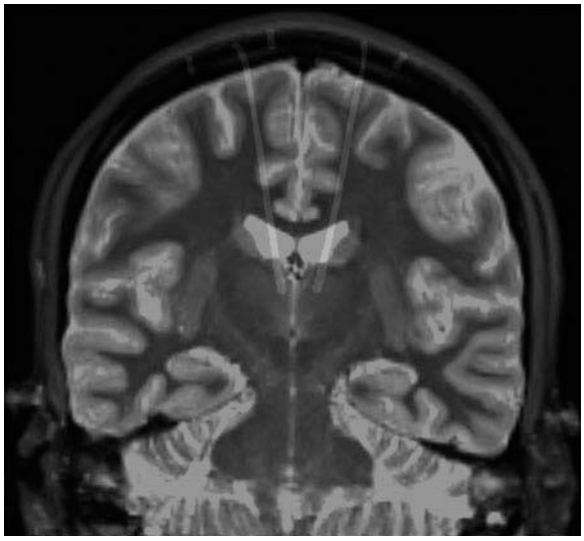

Figure 1. Postoperative computed tomography (CT)–magnetic resonance imaging (MRI) fusion demonstrating a bilateral anterior thalamic nuclei (ANT) implantation, coronal plane.

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

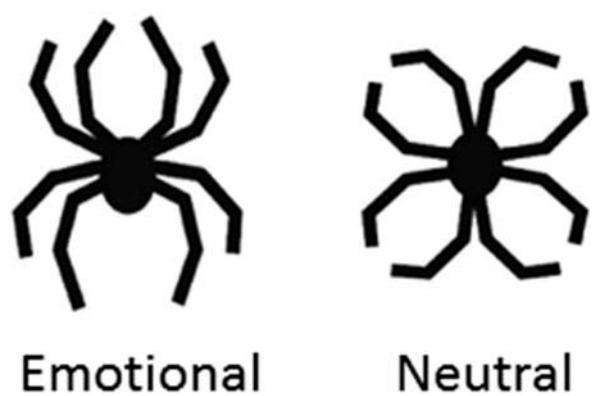

Figure 2. Examples of emotional and neutral distractors. Each distractor is composed of identical elements, which are rearranged to produce either an emotional distractor (spider) or a neutral distractor (flower).

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.

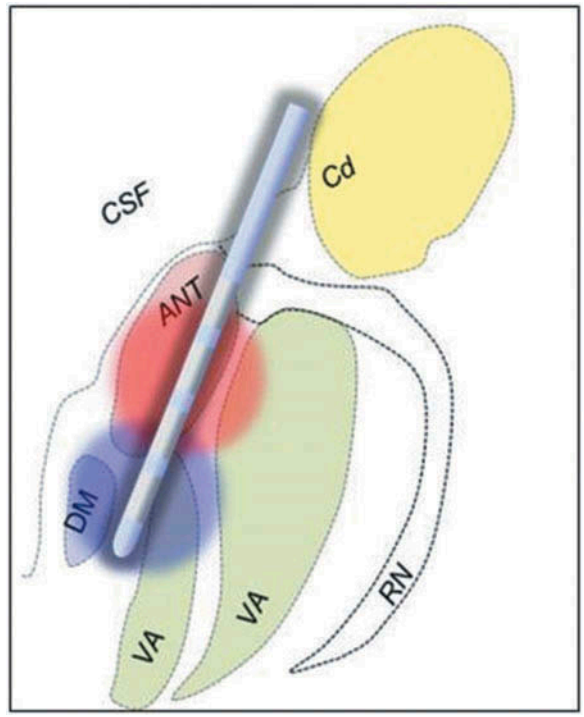

Figure 3. Schematic drawing of deep brain stimulation (DBS) electrode within the anterior thalamus and estimated electric field "at ANT" (red color) and "outside ANT" (purple color), where ANT = anterior thalamic nuclei. Anterior thalamus includes ANT, medial aspect of the ventral anterior nucleus (VA), 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).

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 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% ± 16% varying from 0.44% to 44.6%. The average RT was 527 ms ± 126 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% ± 7.7% in comparison to an error rate of 6.5% ± 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 ± 117 ms) compared to stimulation OFF (504 ± 113 ms), while emotional distractors slowed down RTs (513 ± 116 ms) in comparison to neutral distractors (505 ± 114 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 ON, with slowed RTs in the context of emotional distractors in comparison to neutral distractors during stimulation (emotional 522 ± 119 ms, neutral 505 ± 115), $F(1, 10) = 16.63$, $MSE = 185.4$, $p < .003$, but not during stimulation turned OFF (emotional 504 ± 114 ms, neutral 505 ± 113 ms), $F(1, 10) = 0.16$, $MSE = 243.1$, p = .70 (see Figure 4).

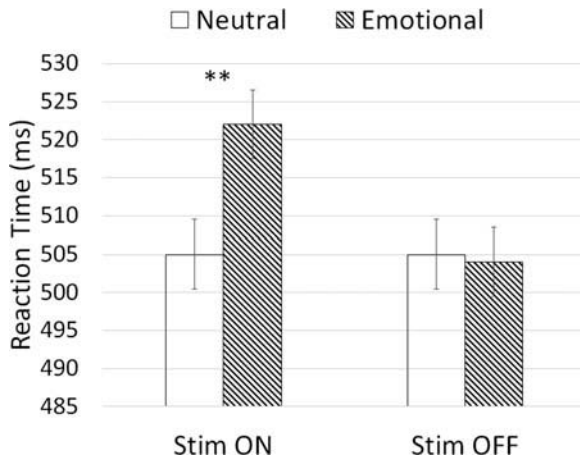

Figure 4. Stimulating the anterior thalamus enhanced attention to threat, as reflected with slowed reaction times (RTs) in the presence of emotional distractors than in the presence of neutral distractors. ANT = anterior thalamic nuclei; Stim = stimulation. **$p < .01$.

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 ± 112 ms) in comparison to stimulation OFF (497 ± 104 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 ± 110 ms, neutral 504 ± 113 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

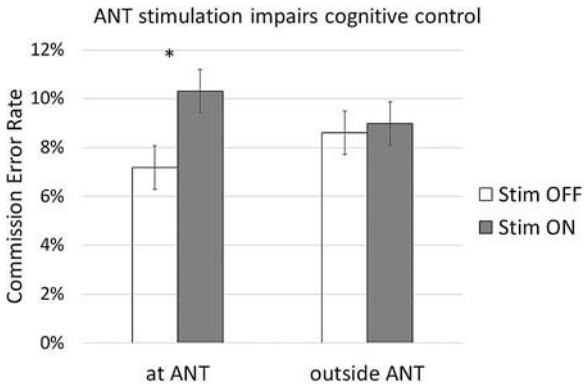

Figure 5. Stimulating the anterior nucleus of thalamus impaired response inhibition, as reflected in increased commission error rate. Stim = stimulation. *$p < .05$.

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% ± 9.16%) than when it was turned OFF (7.17% ± 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% ± 3.03%) compared to stimulation OFF (0.93% ± 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% ± 4.63%) compared to neutral distractors (5.67% ± 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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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.

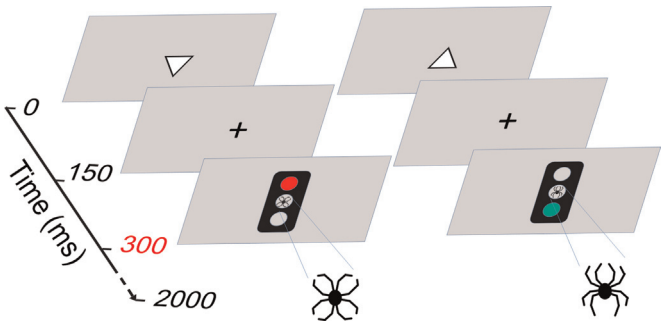

Fig. 1. Schematic presentation of the Executive-RT test. Subjects respond to the orientation of the triangle by a button press in case of a Go-trial indicated by the colour of the traffic light. In the middle of the traffic light there is a task-irrelevant emotional (spider) or emotionally neutral distractor. 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

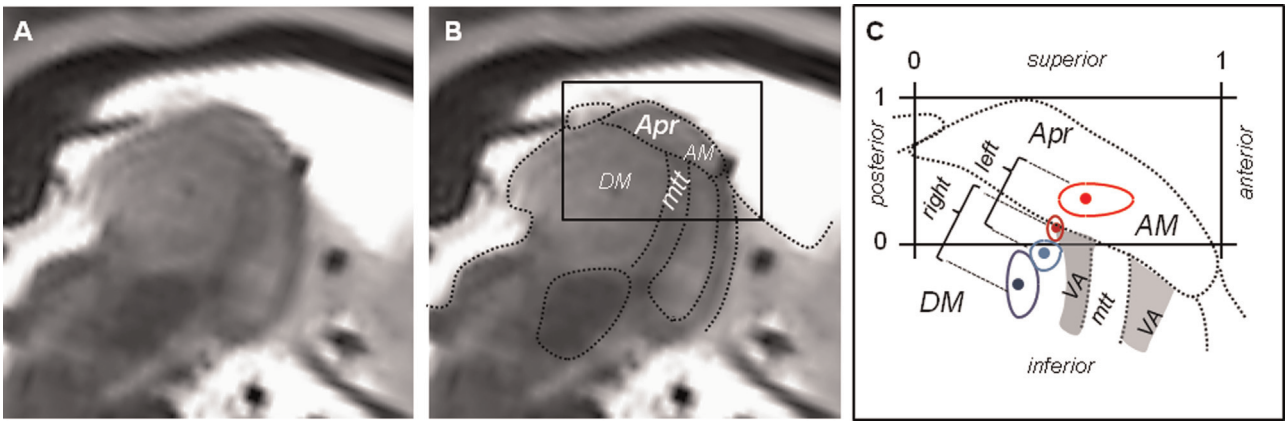

Fig. 2. The visualization of ANT nucleus and locations of stimulation sites in the thalamus. Sagittally oriented 3T MRI STIR image demonstrates the ANT nuclear complex and its subdivisions Apr and AM (A, B). The area shown as a rectangle in the panel B is illustrated in the panel C with higher magnification 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.)

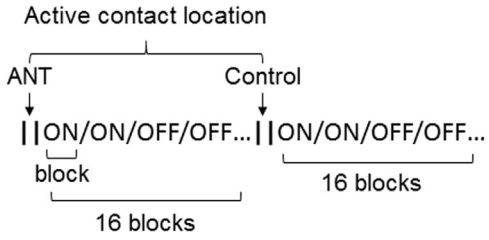

Fig. 3. Illustration of the order of blocks in experimental sessions. The order of the active contact was balanced between subjects. ANT=active contact at ANT, Control=active contact at control location, ON=Stimulation turned on, OFF=Stimulation turned off.

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

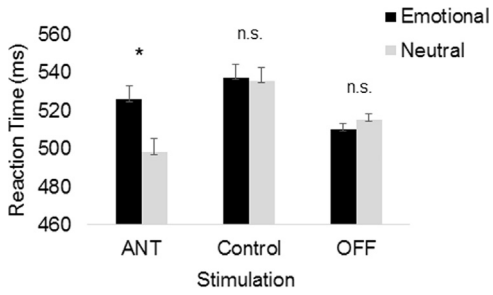

Fig. 4. Increased emotional interference due to ANT–DBS. (A) The RTs were modulated by the valence of the distractors with longer RTs in context of emotional distractors in comparison to neutral distractors when ANT was stimulated. The reaction times did not differ due to emotional valence of the distractor 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

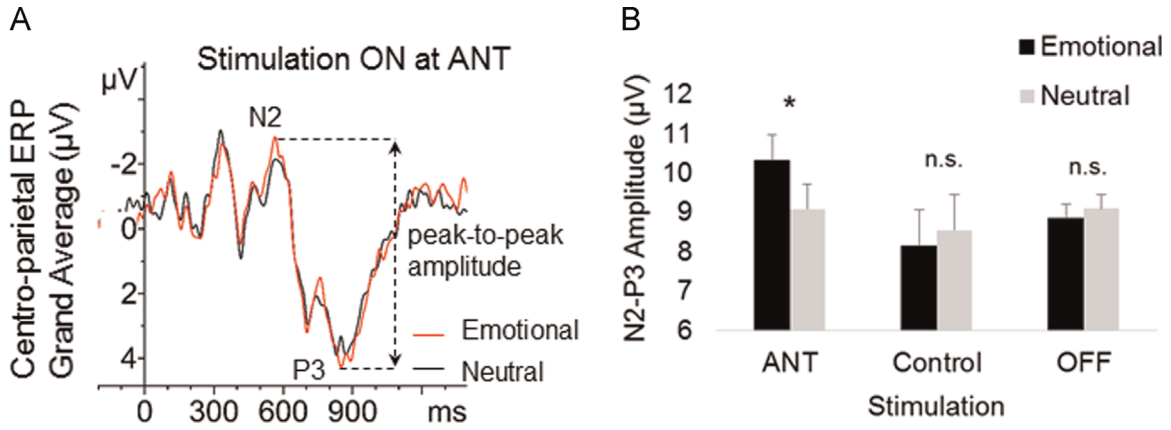

Fig. 5. Increased attention capture by emotional stimuli due to ATN–DBS. (A) Grand average ERP of the centro-parietal region demonstrating N2–P3 peak-to-peak amplitude during ANT stimulation. When ANT was stimulated, N2–P3 peak-to-peak amplitude was increased in context of emotional distractors compared 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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RESEARCH ARTICLE

Human Brain Reacts to Transcranial Extraocular Light

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Abstract

Transcranial extraocular light affects the brains of birds and modulates their seasonal changes in physiology and behavior. However, whether the human brain is sensitive to extraocular light is unknown. To test whether extraocular light has any effect on human brain functioning, we measured brain electrophysiology of 18 young healthy subjects using event-related potentials while they performed a visual attention task embedded with emotional distractors. Extraocular light delivered via ear canals abolished normal emotional modulation of attention related brain responses. With no extraocular light delivered, emotional distractors reduced centro-parietal P300 amplitude compared to neutral distractors. This phenomenon disappeared with extraocular light delivery. Extraocular light delivered through the ear canals was shown to penetrate at the base of the scull of a cadaver. Thus, we have shown that extraocular light impacts human brain functioning calling for further research on the mechanisms of action of light on the human brain.

Introduction

Ambient light guides behavior not only through the traditional visual pathway, but also by regulating numerous nonvisual physiological functions, including circadian, neuroendocrine, neurobehavioral responses and mood [1, 2]. While the main route for light to impact the brain is via photoreceptors on the retina, some birds are known to have deep brain photoreceptors in the hypothalamic and septal regions that react to transcranial extraocular light. These deep brain photoreceptors modulate seasonal changes in physiology and behavior of birds, such as seasonal breading [3, 4]. The effect of extraocular light on reproduction is most commonly studied on birds with eyes and pineal gland surgically removed to avoid ocular light interference. Long-term exposure to light is also needed for measurable changes in physiology [3–5]. Study of extraocular photosensitive proteins led to the discovery of deep brain photoreceptors in birds, e.g. Opsin 5, which detects blue and ultraviolet light and modulates seasonal breeding [3]. However, whether the human brain is sensitive to extraocular light is unknown and a similar approach of studying extraocular photosensitivity of birds is not applicable for humans.

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In animals it has been shown that the skull is not completely impenetrable to light [4, 6] and that the measurable density of skull-penetrated light was found to affect neural metabolism. For example, transcranial bright light has been reported to enhance potassium-induced release of γ-aminobutyric acid (GABA) in cortical neurons of rats [7]. Penetration of light via the skull is also supported in a study showing that covering the head of blind ducks diminished photoperiodicity, where normal testicular growth in response to long daylight stimuli was abolished due to preventing the cranium from exposure to light [8]. Thus, although effect of the extraocular light is subtle it might be important in regulating physiological responses.

Human neuroimaging studies report that exposure to ocular blue light modulates brain activity, higher cognitive functions and emotional brain responses to auditory tasks in visually blind individuals [9–11]. This effect is believed to occur via a novel class of photosensitive retinal ganglion cells distinct from the rods and cones called intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin that is maximally sensitive to short wavelength blue light (~480 nm) [12]. While amphibians, fish, reptiles and birds have been reported to possess deep brain photoreceptors that mediate behavior [13, 14], it is thought mammals lack a similar photosensitive receptor and the evidence for a homologous receptor in mammals remains circumstantial [15–17]. Further, it is neither known whether the comparatively thick human skull bone is penetrable by visible light.

In order to study whether there is any effect of extraocular light on human brain function, we investigated the effect of extraocular light on brain's electrophysiology using event-related potentials (ERPs) and on behavior. ERPs are well suited for studying potential effects of extraocular light on brain physiology with vastly studied components such as the P300 sensitive to attentional and cognitive processes as well as biological and environmental factors [18]. With centro-parietal distribution of the classical P300 or P300b we chose P300 amplitude in the centro-parietal region of interest as a measure for the possible effect of extraocular light. In the present study, transcranial extraocular light was delivered via the ear canals and subject EEG was recorded while they performed a computer based Go/NoGo visual attention task embedded with emotional distractors, i.e. the Executive—Reaction Time (RT) test. Combined with EEG the Executive—RT test allows the study of subtle alterations in attention related brain responses and how they are modulated by emotional stimuli [19–21]. We investigated whether the transcranial extraocular light had any effect on centro-parietal P300 amplitude evoked in the Executive-RT test. Hypothesizing that extraocular light has an effect on brain physiology we expected this effect would be reflected in P300 amplitude and/or performance of the task. We further investigated whether the ear-canal-delivered light could penetrate the base of a skull in a human cadaver.

Methods

Subjects

Eighteen young healthy subjects (mean age = 25 y, sd = 6y, 3 male and 15 female) provided their written consent and voluntarily participated in the study according to the guidelines set forth in the Declaration of Helsinki governing the treatment of human subjects. The study was approved by the Regional Ethical Committee of Tampere University Hospital, Tampere, Finland and the permission number is R12237.

Extraocular light delivery

Extraocular light was delivered using a commercial Bright Light Ear Headset (NPT1100, Valkee Oy, Oulu, Finland; Fig 1A). UV-free and blue-enriched LED light with maximum of 3.5 Lumens was presented via both ear canals. The light has a photon density of 1.13×10^{16}

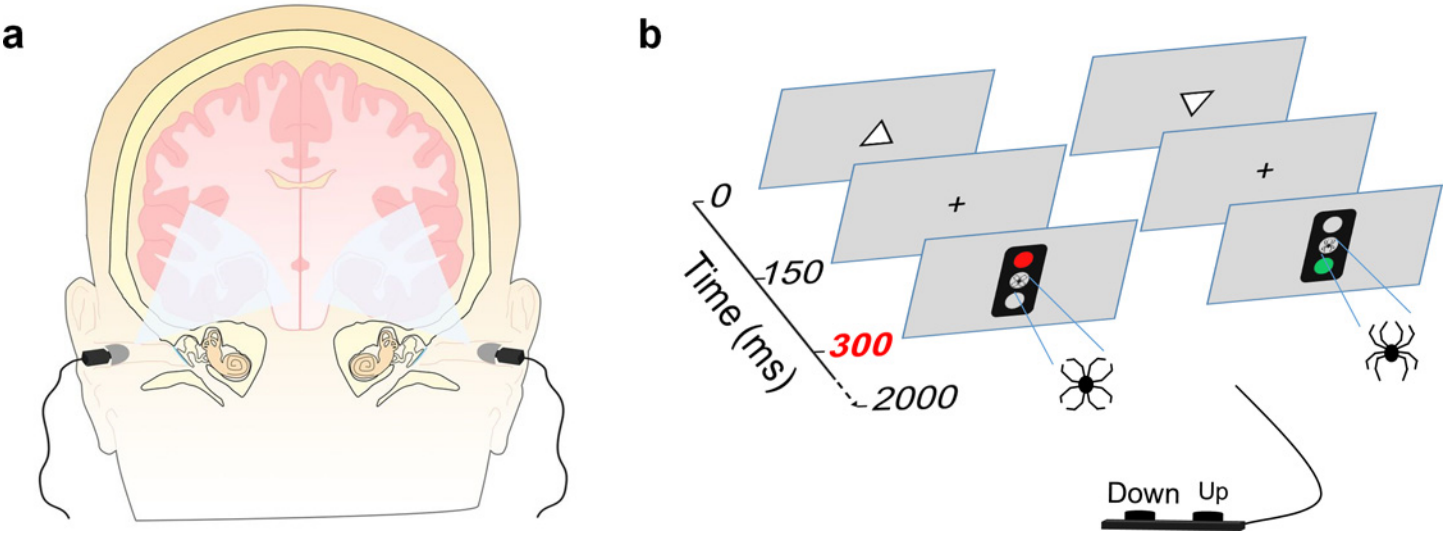

Fig 1. Experimental design. (A) Theoretical penetration of light via ear canals. (B) Schematic presentation of the Executive-RT test. In case of a Go trial subjects were required to report the orientation of a previously presented triangle pointing either up or down with a corresponding button press. In NoGo trials subjects were required to withhold from responding. The Go/NoGo signal was a green or a red traffic light embedded with an emotional (i.e. a line-drawing of a spider) or neutral distractor.

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photons · cm^{-2} · s^{-1} with a peak in the blue region around 448 nm. Detailed information of the LED light can be found in the previous study by Jurvelin et al. [22].

The Behavioral Test

The behavioral test was conducted in a sound-attenuated room under soft white ceiling light. During the behavioral test, i.e. the Executive-RT test (Fig 1B), subjects sat one meter in front of a 21" computer screen. Presentation software (Neurobehavioral System, Inc.) was used to present the visual stimuli and collect the behavioral data. The first visual stimulus is a triangle (pointing either up or down) lasting 150 ms in the center of the screen. Thereafter, there was a 150 ms delay with a fixation cross in the center of the screen before onset of the Go/NoGo signal, i.e. the traffic light. The traffic light was presented for 150 ms leaving approximately 1550 ms for response before the next trial. Each trial lasts for 2000 milliseconds, with each block consisting of 64 trials and a total of 16 blocks. The response rules was switched between each block, i.e. if a green traffic light was the Go signal in the first block, then a red traffic light was the Go signal for the following block. Presented in the middle of the traffic light was a distractor, a schematic drawing in the shape of either a spider (emotional, threatening) or a flower (neutral, non-threatening) [23, 24]. The order of the Go/NoGo signals and the emotional/neutral distractors were randomized.

Prior to testing, the Bright Light headset ear plugs were placed into the ear canals of the subject. When the headset was ON, extraocular light was delivered and when it was OFF, no light was delivered. Light was either ON or OFF for approximately six minutes, thereby allowing subjects to finish two blocks of behavioral tests; thereafter the light status alternated. Eight blocks were completed with ON status and the remaining half of the test completed with OFF status. Subjects did not know whether the ear-canal light delivery was on or off.

EEG recordings and data processing

Continuous electroencephalography (EEG) was recorded using a 64-channel actiCAP Ag/AgCl electrodes (Gilching, Germany) and digitized at 500Hz. Impedance for all electrodes was kept

below 5 kΩ. Common reference was used during recording and in offline EEG data analysis. The offline EEG signal was processed using BrianVision Analyzer 2 (Brain Products, Gilching, Germany) software for event-related potential (ERPs) study. The signal was down sampled to 250Hz. Ocular movement correction was performed using "ICA ocular correction" function of Brain Analyzer 2, where EEG was decomposed into independent components using extended Informax algorithm and components (typically one or two) corresponding to artifact due to ocular movement were rejected. Following this, a band-pass filter (0.01–30 Hz) was applied. After filtering the EEG was then segmented into 2200 ms segments with 200 ms baseline before onset of the trial. The segments were baseline-corrected and processed for further artifact rejection, where segments with EEG amplitude higher than ±70 μV were rejected. ERPs were yielded by averaging the remaining segments for each condition. There were eight condition combinations composed of two types of emotional distractors, two extraocular light statuses and two response types.

ERP amplitude of the centro-parietal brain region of interest (covering electrodes C1, Cz, C2, CP1, CPz, CP2, P1, Pz and P2) was analyzed. In the ERP time window analysis, average amplitude of each 100-ms ERP window was exported for analysis. In P300 peak analysis, P300 peak was detected as the biggest positive peak between 300 ms and 550 ms after onset of the traffic light (i.e. the Go/NoGo signal), corresponding to 600–850 ms on the ERP real-time window. Detected P300 peaks were visually inspected. The P300 amplitude was an average amplitude of 20 ms around the detected peak.

Statistical methods

Repeated-measure-analysis of variance (ANOVA) was used for analyzing ERPs and for reaction times in the behavioral test. Analysis of ERPs, including both analysis of both P300 amplitude and ERP time window analysis, was done using Extraocular light (ON vs. OFF), Emotion (neutral vs. emotional) and Response type (Go vs. NoGo) as factors.

In the reaction time analysis, we only involved trials of correct button press with reaction time longer than 150 ms. Analysis of reaction times was done using Extraocular light and Emotion as factors.

Logistic regression analysis was used for analyzing behavioral error types. Two categories of trials (Go/NoGo) generated three types of errors: incorrect button press (i.e. incorrect report of triangle orientation in Go trial), miss (i.e. no button press in Go trial) and commission errors (i.e. any button press in NoGo trial). Separate binary logistic regression models were generated for each error type. For each error type, trials were dichotomized into either "error" (e.g. incorrect button press in Go trials) or "other" (other outcome of Go trails, i.e. miss or correct response). Subject, Extraocular light, Emotion and interaction between Emotion and Extraocular light were used as predictors.

To account for multiple comparisons, the significance criteria was Bonferroni-adjusted to 0.006. All statistical analysis was performed in using R (version 3.1.3) with ez-package (version 4.2–2) [25].

Skull penetrability to light

We included an autopsy case with the base of skull photographed in order to determine the penetrability of light. This case belongs to the Tampere Sudden Death Study (TSDS), where people died out-of-hospital and underwent medicolegal autopsy at the Department of Forensic Medicine, School of Medicine, University of Tampere. The study protocol was approved by the Regional Ethical Committee of Tampere University Hospital with permission number R09097. In Finland when a study has ethical committee approval and an autopsy is routinely done as is

the case with sudden death, no next of kin consent and no previous permission from the diseased subject or their relatives is required, similarly as previous studies [26–29].

Results

Analysis of centro-parietal P300

Analysis of centro-parietal P300 amplitude revealed a significant interaction between Extraocular light and Emotion, $F(1, 17) = 25.48$, $p = .0001$. Post hoc analysis revealed the main effect of Emotion existed only in situations with no extraocular light delivered, $F(1, 17) = 10.83$, $p = .004$. In contrast, when extraocular light was delivered, no effect of Emotion on P300 amplitude was found, $F(1, 17) = 2.48$, $p = .13$ (Fig 2).

ERP time window analysis

ERP time window analysis with 100-ms windows was also performed for the brain centro-parietal region (see also S1 Text and S1 Table). Analysis of ERP time windows revealed an interaction effect between Emotion and Extraocular light within two consecutive time windows 600–700 ms ($F(1, 17) = 13.22$, $p = .002$) and 700–800 ms ($F(1, 17) = 12.86$, $p = .002$). Post hoc analysis resulted in a main effect of Emotion when Extraocular light was OFF, but not when it was ON (Fig 3). These two consecutive time windows correspond to the latency of P300.

Behavioral analysis

In the behavioral data analysis, no effects were found due to delivery of extraocular light (S2 Text and S2 Table).

Transcranial light penetration via human ear canals

Possible penetration of light through the ear canals was investigated on a human cadaver after the brain was removed upon autopsy. Light penetration of the skull was visible when viewed both in lighted (Fig 4A) and dark (Fig 4B) conditions. Light was able to reach intracranial space through the ear canals and was visible at the base of the skull under the temporal lobes.

Discussion

The present study demonstrates that extraocular light affects human brain functioning. Extraocular light modulated attention-related brain responses, specifically related to emotion-attention interaction. This light abolished emotional modulation of centro-parietal P300 brain response suggesting the extraocular photosensitivity of the brain. The light was able to penetrate the base of the skull and reach the brain's temporal lobes, as demonstrated in a human cadaver (Fig 4). Uncovering the subtle effect of extraocular light leads to new insight of human brain functioning.

We confirmed in our investigation of a human cadaver skull that light is capable of penetrating the human skull via ear canals and reach the temporal lobe of the brain. Because the brain is floating in cerebrospinal fluid, transmitted light might be widely dispersed, thus illuminating the basal surface of temporal lobe. The mechanism by which extraocular light may affect human brain functioning is unclear.

There might be several mechanisms of action of light on brain function depending on species, cell type and the physical properties of light. Deep brain photosensitive molecules OPN3 and OPN5 have been shown in mice and birds acting as signal transmitters for light [3, 30, 31]. Visible light has been reported to enhance potassium induced release of the neurotransmitter GABA of cortical neurons of rats [7]. On the other hand, near-infrared (NIR) light, found to

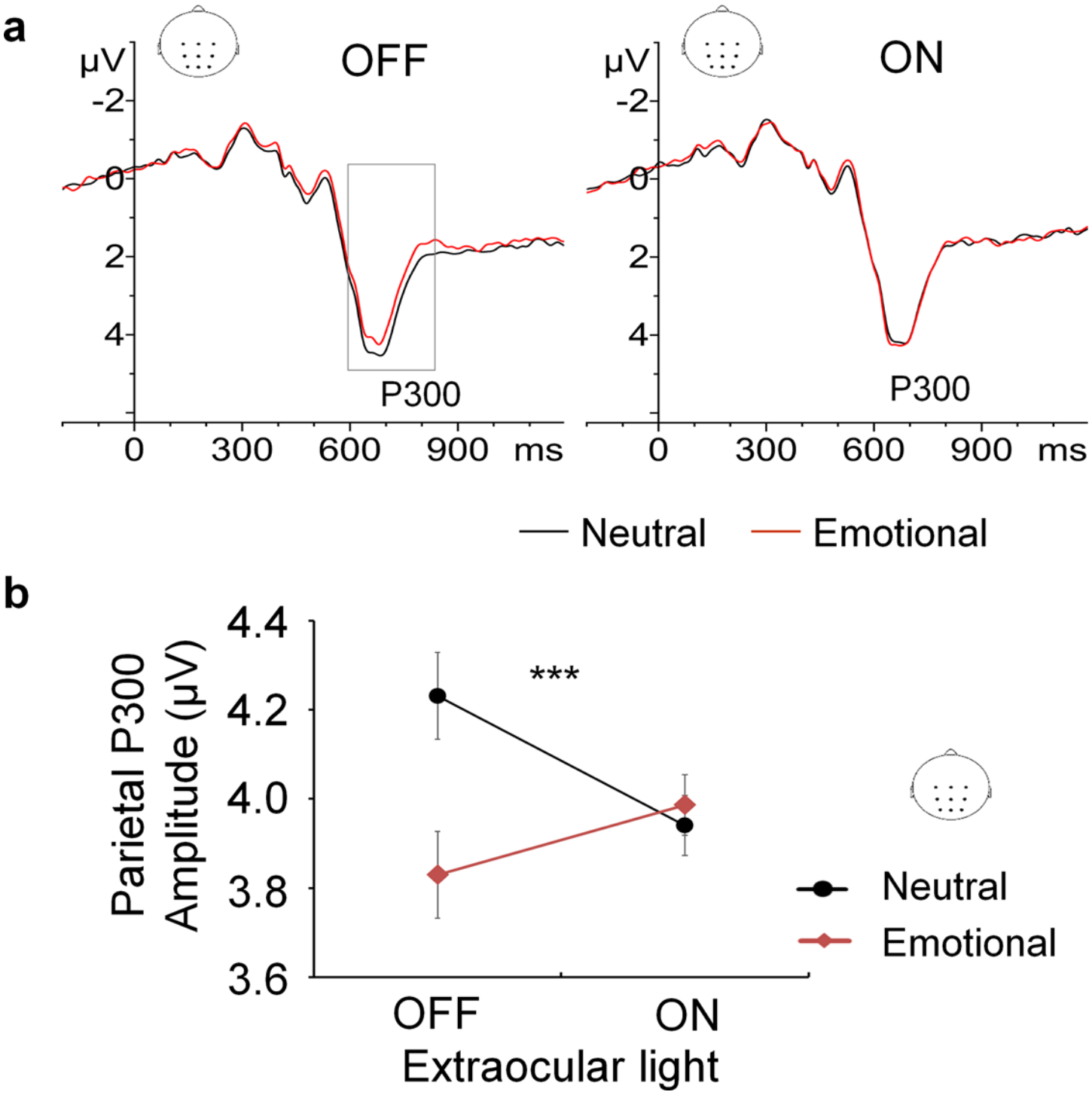

Fig 2. The effect of extraocular light on emotional modulation of P300 amplitude. (A) Grand-average ERP of the centro-parietal region. When extraocular light was OFF, emotional distractors diminished P300 amplitude compared to neutral distractors. When extraocular light was ON the valence of the distractor had no effect on the P300 amplitude. (B) Extraocular light abolished the normal emotional modulation of centro-parietal P300 amplitude. This effect was highly significant (p = .0001). Error bars: Fisher's least significant difference.

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increase adenosine triphosphate production in mitochondria, modulate reactive oxygen species and induce cellular transcription factors [32, 33]. NIR also penetrates human skull [34] and is used to study human brain hemodynamics (NIR spectroscopy) [35]. Furthermore, transcranial NIR has been studied as a potential therapy to treat mild traumatic brain injuries [36, 37].

Event-related potentials provide online information of brain functioning even with no behavioral changes [38–40]. In our study, ERP analysis revealed that extraocular light

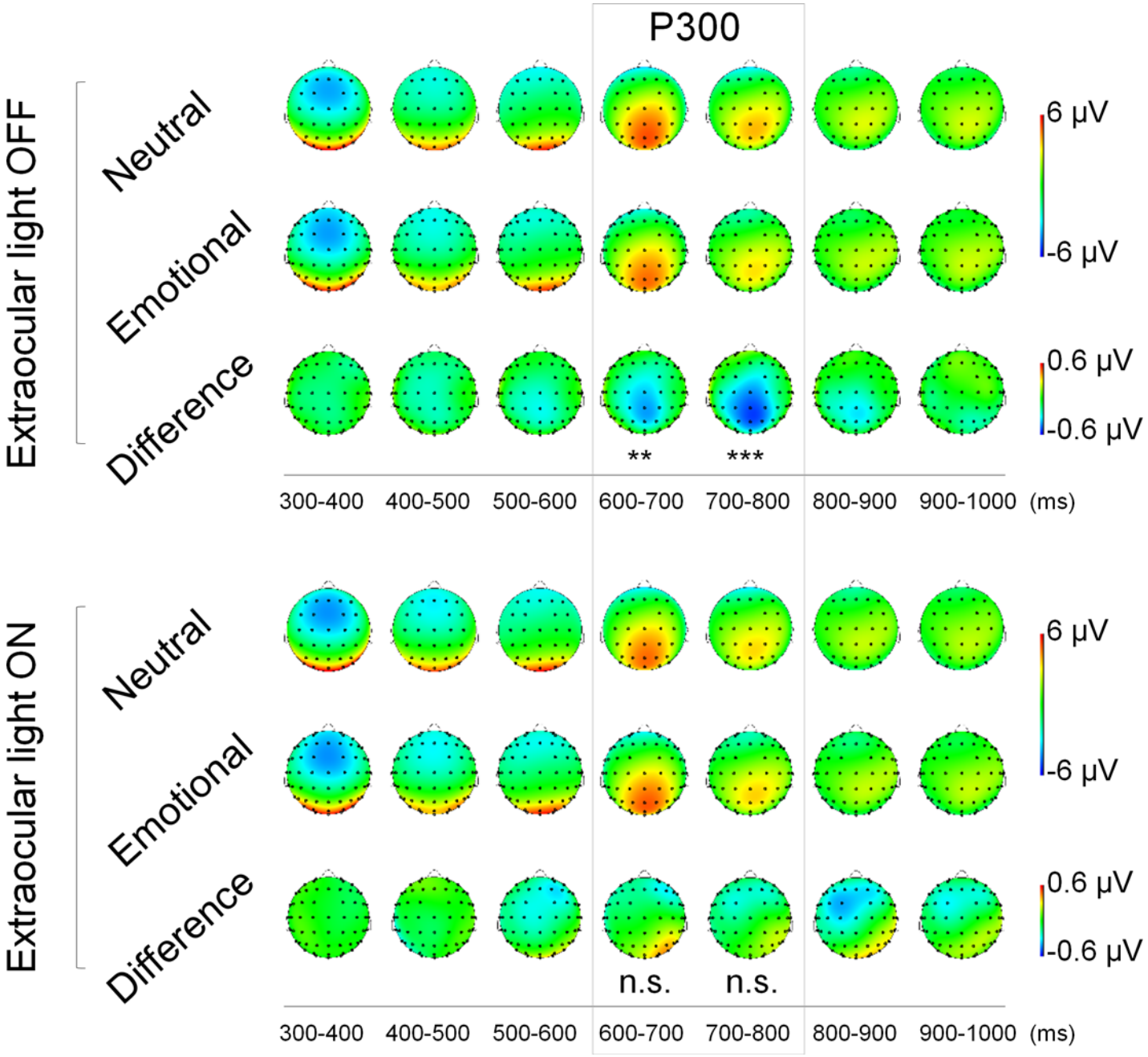

Fig 3. Extraocular light abolished the normal emotional modulation of attention related ERPs at 600–800 ms (corresponding to the 300–500 ms after Go/NoGo signal). When extraocular light was OFF (upper panel), the valence of the distractor had an effect on the ERP waveforms with Difference waveform (Emotional-Neutral) leading to centro-parietal negativity at 600–800ms. In contrast when extraocular light was ON (lower panel) the valence of the distractor did not have a significant effect on ERPs. The main effect of Emotion is marked; n.s. = no significance.

doi:10.1371/journal.pone.0149525.g003

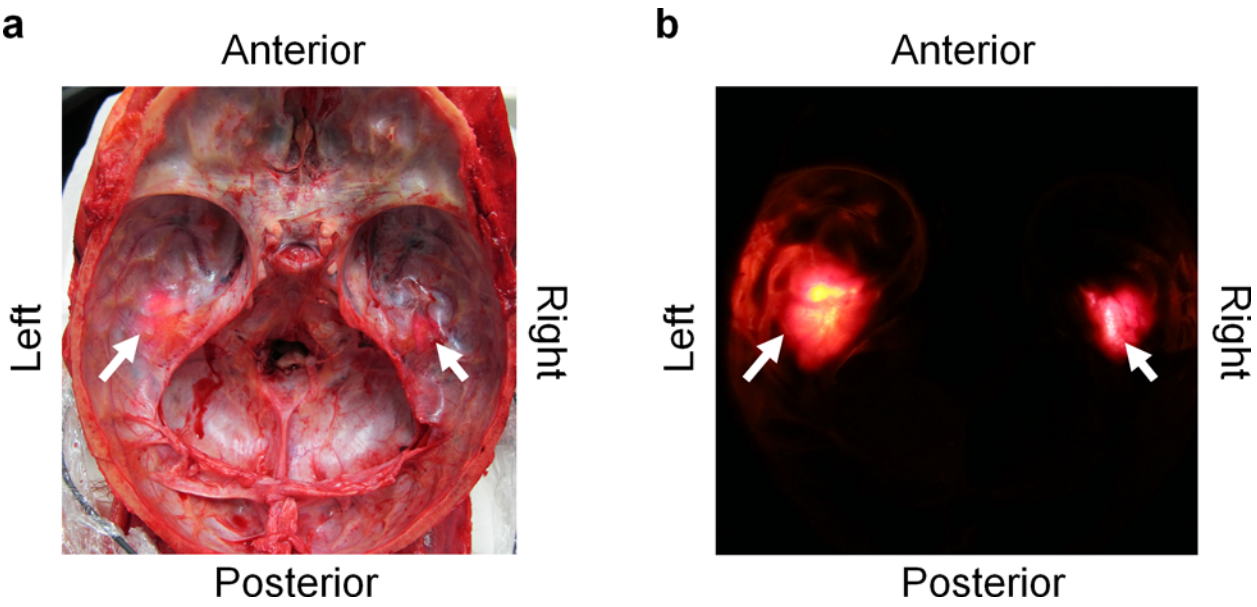

Fig 4. Light is able to penetrate human skull via ear canals. (A) Light penetration through the ear canals at the base of the scull on a cadaver after inserting the Bright Light Ear Headset into both ear canals under normal surgical lights in the autopsy room and (B) same skull base after turning the surgical lights off and darkening the room.

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abolished the modulatory effect of emotion typically found on P300 amplitude [41–44]. This finding is consistent with previous EEG and fMRI studies showing changes in brain activity with ocular blue light exposure of less than a minute in visually blind subjects performing an auditory task [9]. Meanwhile, exposure to extraocular light delivered via the auditory canal did not alter performance on an Executive-RT task engaging several executive functions with threat-related and emotionally neutral distractors. The lack of behavioral signs might be due to extraocular light effects being subtle and the insensitive nature of behavioral measures. This is also in line with a previous study by Bromundt et al using light delivered via the auditory canal that found no evidence of performance improvement on a 10-minute psychomotor vigilance task [16]. Nevertheless, brain neuroimaging findings of these subtle effects, both due to extra-ocular and ocular light exposure, are likely to be demonstrated only when subjects are actively engaged in a cognitive task as was the case in our study and the previous ones [9, 10].

Beyond the apparent consistency with previous findings [9, 10, 16], uncovering the extraocular pathway of light in the human brain is revolutionary. With extraocular bright light delivery via both ear canals, centro-parietal P300 responds differently toward emotional distractors, indicating that the human brain reacts to extraocular light. The centro-parietal P300 has been associated with attentional resource allocation [45], with emotional stimuli able to capture attentional resources [19, 23, 46] and modulate centro-parietal P300 amplitude [41–43]. The emotional modulation of centro-parietal P300 amplitude due to emotional distractors disappeared during extra-ocular light delivery. Thus, extraocular light modulated emotion-attention interaction.

The current study has demonstrated that extraocular light has immediate effects on brain potentials of healthy subjects. Uncovering that brain functions may be modulated by extraocular bright light has broad implications for future research on brain physiology. Furthermore, our findings might also promote investigation on potential clinical applications. Whether chronic bright light delivery via the ear canals bears clinically applicable benefits is beyond the scope of this study. Transcranial bright light treatment has been previously reported by Jurvelin

et al to relieve depressive symptoms associated with seasonal affective disorder [47]. While the study by Jurvelin et al lacked an adequate placebo control group and there was no dosage effect, the results suggested that transcranial light might impact mood. The current findings showing altered emotion-attention interaction due to transcranial light is consistent with potential effect of bright light on mood.

In conclusion, we have found that extraocular light impacts human brain physiology. Whether similar photosensitive brain receptors exist in the human brain as in birds is still unclear. The results from this study call for future research on the mechanism of action of light on the human brain. Demonstrating how extraocular light influences emotional reactivity might provide additional insights regarding how light directly affects mood [2]. The subtle effect of extraocular light might be critical for healthy human brain functions and disease. Therefore, the results from this study have potential widespread impact on understanding the effect of light on the healthy brain as well as its potential involvement in brain disorders.

Supporting Information

S1 Table. List of p values for the analysis of ERP time windows.
(DOCX)

S2 Table. Logistic regression analysis of error types did not reveal significant predictors.
(DOCX)

S1 Text. Analysis of Event-related potential data.
(DOCX)

S2 Text. Analysis of reaction times.
(DOCX)

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Author Contributions

Conceived and designed the experiments: KHO PJK KMH. Performed the experiments: KMH. Analyzed the data: LS JP AK. Contributed reagents/materials/analysis tools: JP. Wrote the paper: LS JP KHO PJK KMH.

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