Epilepsy & Behavior 64 (2016) 171–179

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

The effect of vagus nerve stimulation on response inhibition

Hanne Schevernels [a,*], Marlies E. van Bochove [b], Leen De Taeye [c], Klaas Bombeke [a], Kristl Vonck [c], Dirk Van Roost [d], Veerle De Herdt [c], Patrick Santens [e], Robrecht Raedt [c], C. Nico Boehler [a]

[a] Department of Experimental Psychology, Ghent University, 9000 Ghent, Belgium
[b] Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, 6525 HR Nijmegen, The Netherlands
[c] Laboratory for Clinical and Experimental Neurophysiology, Neurobiology and Neuropsychology (LCEN3), Ghent University, 9000 Ghent, Belgium
[d] Department of Neurosurgery, Ghent University Hospital, 9000 Ghent, Belgium
[e] Department of Neurology, Ghent University Hospital, 9000 Gent, Belgium

ARTICLE INFO

Article history:
Received 23 November 2015
Revised 27 August 2016
Accepted 6 September 2016
Available online 12 October 2016

Keywords:
Epilepsy
Vagus nerve stimulation
Response inhibition
Norepinephrine
Event-related potentials
Pupil size

ABSTRACT

In the current study, we explored whether vagus nerve stimulation (VNS) in patients with epilepsy, which is believed to increase norepinephrine (NE) levels via activation of the locus coeruleus, would positively affect response inhibition. Moreover, we tried to identify the dynamics of the underlying neural processes by investigating event-related potentials (ERPs) and pupil size. Patients performed a stop-signal task once when stimulation was switched on and once when it was switched off. We found a correlational pattern suggesting that patients who clinically benefit more from VNS treatment also show a larger behavioral advantage, in terms of faster response inhibition, when the vagus nerve is being stimulated. Event-related potential (ERP) results suggested more pronounced reactive inhibition when stimulation was switched on, independent of the individual amount of seizure reduction. Transient go-locked pupil size was increased from go trials to successful stop trials to unsuccessful stop trials but without displaying a clear VNS effect, which however, might relate to limited sensitivity. We conclude that VNS likely has a positive effect on response inhibition, at least in patients with epilepsy that benefit clinically from the treatment, presumably relating to enhancements of response-inhibition mechanisms and, therefore, identify enhanced response inhibition as a possible cognitive benefit of VNS.

1. Introduction

For successful navigation of everyday life situations, it is important to be able to rapidly inhibit a response when the current action is no longer appropriate or even detrimental. In psychological research, response inhibition has frequently been investigated using the stop-signal task [1]. In this task, a go stimulus is usually presented to which subjects have to respond quickly by pressing a button. However, occasionally, a stop signal is displayed rapidly after the go stimulus, in which case responses are to be withheld. Hence, in stop trials, action-related processes that were already initiated by the go stimulus need to be suppressed. Importantly, by implementing this task, one can estimate the stop-signal reaction time (SSRT), which is an index of the time needed for a patient to inhibit a response. This estimation is usually based on a horse-race model assuming that there is a competition between two parallel processes (going and stopping), and whichever process finishes first will determine the behavioral outcome [2,3] (see also [4]). Studies have found longer SSRTs and/or decreased stopping success in people with attention-deficit hyperactivity disorder (ADHD; [5–7]), Parkinson's Disease [8], and obsessive–compulsive disorder [9]. In parallel, research has begun to identify the neuroanatomical networks that underlie inhibitory control, and the consensus seems to be that prefrontal areas in the right inferior frontal gyrus (IFG) and/or the pre-supplementary motor area (pre-SMA) interact with motoric parts of the basal ganglia in order to cancel a motor response [10–12].

In addition to the neuroanatomical substrates, research has investigated which neurotransmitters play a modulating role in response inhibition. Here, particularly norepinephrine (NE) has been shown to play a significant role (for an overview see [13]). Specifically, performance in the stop-signal task in both animals and humans has been found to improve from medication that increases extracellular levels of NE, like atomoxetine [14–17] and methylphenidate [18]. Moreover, patients with ADHD, who are generally impaired in inhibition capabilities and are simultaneously assumed to suffer from insufficient NE levels, show improved response inhibition when medicated with drugs that boost NE, like desipramine and methylphenidate [19,20]. Similarly, certain doses of guanfacine impair stopping probably via a decrease in NE release [16,21]; but see [22]. However, many of these drugs also affect

Abbreviations: SSRT, stop-signal reaction time; ADHD, attention-deficit hyperactivity disorder; IFG, inferior frontal gyrus; pre-SMA, pre-supplementary motor area; NE, norepinephrine; DA, dopamine; VNS, vagus nerve stimulation; LC, locus coeruleus; EEG, electroencephalogram; ERP, event-related potential; CSD, current source density; AED, antiepileptic drug.

* Corresponding author at: Dept. of Experimental Psychology, Ghent University, Henri Dunantlaan 2, 9000 Ghent, Belgium.
E-mail address: h.schevernels@gmail.com (H. Schevernels).

http://dx.doi.org/10.1016/j.yebeh.2016.09.014
1525-5050/

the levels of other neurotransmitters, in particular, dopamine (DA) (see e.g., [23]), but also serotonin, acetylcholine, and histamine [24–26]. Yet, results of recent studies suggest that inhibitory performance in the stop-signal task is mostly sensitive to fluctuations in NE levels [13,16,21,27].

In the current study, the involvement of NE in response inhibition was further investigated by indirectly manipulating NE levels in patients that are treated with vagus nerve stimulation (VNS). Vagus nerve stimulation is applied in suitable patients with drug-resistant epilepsy. It entails a spiral electrode that is wrapped around the left vagus nerve in the neck and connected to and controlled by a pulse generator that is implanted below the skin. In about 50% of the patients, VNS successfully reduces the amount of seizures by a significant degree (≥50%) [28]. Unfortunately, it is still unclear why VNS has therapeutic effects in some patients (VNS responders), while there is a complete lack of therapeutic effect in others (VNS nonresponders), and there is still no predictive biomarker available for therapeutic effect of VNS, which would allow selecting only those patients in which VNS will have an antiepileptic effect. Although it is not clear exactly how VNS suppresses epileptic seizures, experimental evidence suggests that the NE system plays an important role, consistent with the fact that vagus nerve fibers connect via the nucleus of the solitary tract through two di-synaptic pathways to the locus coeruleus (LC), which is the main source for NE in the forebrain [29]: one via fibers containing excitatory amino acids from the nucleus paragigantocellularis, and one via inhibitory fibers containing GABA from the nucleus prepositus hypoglossi, (for an extensive review, see [30]). Accordingly, animal studies have found that VNS enhances NE concentrations in several brain areas like the cortex, nucleus accumbens, and hippocampus [31–33].

There is a substantial amount of data supporting a crucial role for the LC–NE system in the anticonvulsant effects of VNS. For example, when the LC is lesioned, using the selective neurotoxin DSP-4, anticonvulsant effects of VNS are blocked [34]. Furthermore, blocking alpha2 adrenoreceptors using SKF-86466 partially reverses the anticonvulsant effects of VNS [31]. Substantial additional evidence also points at a potent inhibitory effect of NE on seizures and epilepsy (for review, see [35]). In particular, it appears that the activity of LC is critical in limiting the spreading and duration of seizures since damage to LC neurons is able to convert sporadic seizures into status epilepticus [36]. In addition, impaired LC–NE signaling increases neuronal damage by status epilepticus and leads to neuronal plasticity changes that increase the risk of developing epileptic brain networks and chronic epilepsy [37]. These epilepsy-modifying effects have been related to the effects of LC–NE signaling on cortical excitability via modulation of synaptic plasticity, memory, and gene expression [35,37–40]. Although results are not fully conclusive, LC-dependent synaptic plasticity as well as more short-term effects of cortical excitability might underlie positive effects of VNS on depression, cognition, and memory (for reviews, see [35,41]). Taken together with the empirical support from earlier studies that have manipulated NE levels using drugs, we hypothesized that response inhibition would be enhanced when the LC–NE system is triggered via VNS.

In addition to behavioral measures of response inhibition like the SSRT, we also studied electroencephalographic (EEG) signals related to response inhibition given that event-related potentials (ERPs) have generally been shown to be sensitive to VNS [42–44], but see [45]. Studies applying EEG in the stop-signal task usually focus on the stop N2 component, which peaks around 200 ms after the stop-signal at frontal electrodes, and the stop-evoked frontocentral P3 that is maximal at approximately 300 ms. Although there is still debate about which cognitive functions are underlying the stop N2, usually, the stop N2 has been related to error detection and performance monitoring, given that the N2 amplitude has been found to be larger in unsuccessful stop trials compared with successful stop trials [46–49], but see [50,51]. Typically, the dopaminergic system has been found to be involved in behavioral and error monitoring [27,52,53], but recently, it was pointed out that also other neurotransmitters including NE might play a role in performance monitoring [54]. Hence, it is not clear whether VNS will affect the stop-evoked N2. In contrast to the N2, the frontal P3 is increased in successful stop trials and believed to reflect actual response inhibition and/or the evaluation thereof [46,47,55–57]. Hence, given the previously mentioned involvement of NE in response inhibition, we expected that VNS would have an influence in particular on P3 amplitudes. Both the N2 and P3 components have also been shown to peak earlier when stopping was successful suggesting an earlier internal response to the stop signal [58–60], and therefore, we also analyzed peak latencies.

Furthermore, response inhibition performance might not only depend on reactive inhibitory processes but also on the attentive processing of the task-relevant stimuli. Therefore, we investigated the sensory/attentional N1 components related to the processing of both the visual go stimulus and the auditory stop signal. The amplitude of the stop-evoked N1 has been found to be increased in stop trials that end up being successful, implicating varying levels of attention directed to the stop signal in stopping success ([55,56,61,62]; but see [63] for an inhibition-related account of the N1 component). In unmedicated adults with ADHD, Bekker et al. showed that this difference could not be observed, indicating that disrupted attentional processing might also contribute to impaired stopping in these patients [62], but subsequent work by Overtoom et al. found that such a relationship could be restored by administering methylphenidate [64]. In addition, the N1 related to processing of the go stimulus has been observed to be enhanced in unsuccessful stop trials suggesting that more attention to the go stimulus is more likely to result in unsuccessful stopping [61], see also [65]. Boehler et al. concluded that changes in attentional resource allocation can be made within and between trials, and that stopping success is dependent on the level of attention devoted to the go stimulus and the stop signal in each trial [61]. Since the NE system is supposed to also be involved in attention and sensory processing [66], N1 components might be sensitive to changes in NE levels induced by VNS.

To further support the idea that VNS affects response inhibition via the NE pathway, we also examined pupil dilation given that pupil size is closely linked to the LC [67] and has been used as a marker of the amount of NE in the brain [68,69]. Moreover, VNS has been shown to enhance resting pupil size [70]. Hence, in the current study, we compared behavioral, ERP and pupil measurements in the stop-signal task in patients with epilepsy that were implanted with VNS when stimulation was switched on versus off, as an indirect way to further explore the role of the NE system in response inhibition.

2. Materials and methods

2.1. Patients

After giving written informed consent, twenty patients with refractory epilepsy (8 males, mean age = 44 years, range = 21–66 years) participated in the current experiment. The study was approved by the ethics board of Ghent University Hospital. All patients were treated with VNS stimulation for at least 18 months and did not show any signs of mental retardation. Seizure reduction following VNS was calculated by subtracting the number of seizures during three consecutive months preceding our test period (after VNS implantation) from the number of seizures in the three months before VNS implantation (baseline), divided by the number of seizures in the three months before VNS implantation (baseline).[1] A detailed description of this and other patient characteristics is provided in Appendix 1. We note that the current study was part of a set of experiments that were performed successively by all patients (for an additional report on the same cohort, see [42]).

[1] In case the number of monthly seizures decreased by more than 50% after VNS implantation, patients were considered responders to the VNS therapy (n = 10), and patient recruitment generally aimed to match the number of responders and nonresponders.