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Reduced distractor interference during vagus nerve stimulation

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ABSTRACT

Suppressing irrelevant information in decision making is an essential everyday skill. We studied whether this ability could be improved in epileptic patients during vagus nerve stimulation (VNS). VNS is known to increase norepinephrine (NE) in the brain. NE is thought to improve several aspects of cognitive control, including the suppression of irrelevant information. Nineteen epileptic VNS patients executed the Eriksen flanker task twice, both during on and off stimulation. Distractor interference was indexed by the congruency effect, a standard empirical marker of cognitive control. We found a reduced congruency effect during stimulation, which indicates an improved ability to suppress distractor interference. This effect was only found in patients that are clinically determined VNS-responders (n = 10). As VNS increases NE in VNS-responders, our finding suggests a beneficial role of NE in cognitive control. At the same time, it suggests that VNS does not only reduce seizure frequency in epileptic patients, but also improves cognitive control.

1. Introduction

We frequently have to make choices from multiple response options while the appropriate response is not always the most obvious one. The ability to choose the appropriate response and ignore distractors is an important aspect of cognitive control.

Many studies investigating cognitive control focus on cortical structures as the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (dLPFC). Besides these, there are prominent subcortical contributions to cognitive control. Dopamine has since long been considered important (Braver and Cohen, 2000; Cools and D'Esposito, 2011; Montague et al., 1996; Schultz, 1998). However, recent years have witnessed an increasing interest in a possible role of norepinephrine (NE) in cognitive control, a neuromodulator originating from the brainstem locus coeruleus (LC) (Arnsten, 1998; Aston-Jones and Cohen, 2005; Eldar et al., 2013; Nieuwenhuis and Jepma, 2011; Sara, 2009; Verguts and Notebaert, 2008, 2009). Simultaneously the interest in positive cognitive side-effects of vagus nerve stimulation (VNS) in epileptic patients has increased (Vonck et al., 2014). VNS is known to reduce seizure frequency in epileptic patients through increased NE (Raedt et al., 2011). These findings lead to the current study, in which we concurrently study the role of NE in cognitive control and the improvement of cognitive control in epileptic patients through VNS.

For drug-resistant epileptic patients for whom surgical removal of the epileptogenic zone is not possible, VNS is an available therapy. For VNS, an electrode is placed around the left vagus nerve in the neck. The afferent vagus fibers project to the brainstem Nucleus Tractus Solitarii (NTS) which in turn projects both directly and indirectly to the LC (George and Aston-Jones, 2010; Van Bockstaele et al., 1999). VNS increases NE in the hippocampus (Raedt et al., 2011), amygdala (Hassert et al., 2004) and cortex (Roosevelt et al., 2006). VNS reduces epileptic seizures (Ben-Menachem, 2002; Ben-Menachem et al., 2015; DeGiorgio et al., 2000; Weinshenker and Szot, 2002) and improves cognition (Clark et al., 1999; Dodrill, 1986; Grill and Ng, 2010; Helmstaedter et al., 2001; Martin et al., 2004; Vonck et al., 2014). Lesioning the LC eliminates the seizure suppressive effect of VNS (Krahl et al., 1998) underlining the role of the LC (and consequently NE) in VNS. Moreover, three fMRI studies with transcutaneous VNS (tVNS) in healthy humans show increased LC activation during stimulation (Dietrich et al., 2008; Frangos et al., 2015; Yakunina et al., 2017). In tVNS the vagus nerve is stimulated non-invasively through the left outer ear where the afferent auricular branch of the vagus nerve ends (Ventureyra, 2000). For yet unknown reasons, not all VNS patients benefit from this treatment. A VNS patient is medically considered a responder when there is a monthly seizure frequency reduction of at least 50% compared to pre-

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Table 1
Patient characteristics. Abbreviations: R = responder, NR = non-responder, Impl = implantation, HEZ = hypothesized epileptogenic zone, FL = frontal lobe, TL = temporal lobe, PL = parietal lobe, OL = occipital lobe; AEDs = anti-epileptic drugs: CBZ = carbamazepine, CLB = clobazam, CZP = clonazepam, LCZ = lacosamide, LTG = lamotrigine, LEV = levetiracetam, OXC = oxcarbazepine, PB = phenobarbital, PHT = phenytoin, PGB = pregabalin, RG = retigabine, VPA = valproic acid, VGB = vigabatrin.

Patient	Sex	Age (years)	Seizure reduction (%)	Seizure frequency pre-VNS	VNS Impl Year	VNS Parameters			HEZ		AEDs
						Output (mA)	Frequency (Hz)	Pulsewidth (μs)	Lobe	Side	
Responders											
R_1	M	52	100.0	4	1995	2.00	30	500	TL	Bilateral	VPA, VGB, CBZ
R_2	F	57	100.0	2	1997	1.50	30	500	FL + TL + PL	Right	LTG
R_3	F	52	100.0	5	2003	2.50	30	500	TL	right	LEV, CBZ
R_4	M	22	100.0	17	2007	0.75	20	500	General	bilateral	VPA, LTG
R_5	M	36	95.6	45	2010	2.25	20	250	FL	right	LEV, PGB, CZP
R_6	F	66	95.0	60	2003	2.50	20	500	General	bilateral	LEV, LTG, CZP
R_7	F	55	85.0	20	2002	3.00	20	500	TL	right	LEV, LTG, CBZ
R_8	F	45	73.3	45	1997	2.75	20	250	TL	right	LEV, LTG, CZP
R_9	F	30	63.3	30	2005	2.50	25	500	General	bilateral	VPA, LEV, PGB, CZP
R_10	F	21	54.5	165	2009	3.00	30	500	General	bilateral	VPA, LTG, PGB, LCZ
Mean		**44**	**86.7**	**39.3**	**2003**	**2.28**	**25**	**450**			
Non-responders											
NR_1	M	55	46.9	32	2003	2.75	30	500	FL + TL	bilateral	PHT, LCZ
NR_2	M	61	33.3	30	1999	2.5	20	500	FL	bilateral	CBZ, PB, LEV, PGB, CZP
NR_3	M	53	9.1	66	2007	2.75	30	500	FL + PL	bilateral	VPA, LTG
NR_4	M	23	3.1	32	2007	2.75	30	500	FL + PL	bilateral	LTG, CZP, OXC, LCZ
NR_5	M	25	0.0	4	2008	2	30	500	OL	left	LEV, CZP, CBZ
NR_6	F	32	0.0	9	2007	2	20	250	FL + OL	right	LEV, CZP, CBZ
NR_7	F	30	0.0	180	2011	0.75	20	250	FL + TL + PL	left	CLB, CZP, OXC
NR_8	F	54	0.0	99	2010	2.75	20	500	FL	left	CZP, CBZ, RG, LCZ
NR_9	F	48	0.0	75	2010	1.75	30	500	FL	left	VPA, LEV, PB, LCZ
Mean		**42**	**10.3**	**58.6**	**2007**	**2.19**	**26**	**445**			

VNS therapy. A study of 195 VNS patients shows a responder rate of 35% (DeGiorgio et al., 2000), and another study ($N = 138$) shows a responder rate of 59% (De Herdt et al., 2007). Several studies have used VNS to investigate the role of NE in various aspects in cognition such as auditory oddball detection (De Taeye et al., 2014), improved response inhibition (Schevernels et al., 2016), and in applying cognitive control following the commission of an error (Sellaro et al., 2015).

Although previous research shows the effect of VNS on several aspects of cognition, its effect in cognitive control remains unclear. The ACC, known for its role in detecting the need for increased cognitive control (Botvinick et al., 2001), is connected to the LC (Arnsten and Goldman-Rakic, 1984; Jodo et al., 1998) and can therefore activate the LC. The LC is the main source of NE in the cortex (Berridge and Waterhouse, 2003; Sara, 2009; Sara and Bouret, 2012). Cognitive control might improve from ACC-triggered increased NE release, perhaps via increased signal-to-noise ratio (SNR; Aston-Jones and Cohen, 2005). The interference of distractors would subsequently be reduced. This would reduce the difference in RTs between trials with congruent distractors and incongruent distractors, which is called the congruency effect. Furthermore, cognitive control might improve through increased Hebbian learning between stimulus and response representations (Verguts and Notebaert, 2008, 2009). Previously encountered distractors might be better ignored as the association between action target and the appropriate response might be better learned. This would result in a smaller congruency effect following a trial with incongruent distractors compared to the congruency effect following a trial with congruent distractors, which is called the sequential congruency effect (SCE). Increased NE release might improve this learning process (Berridge and Waterhouse, 2003; Harley, 2004; Sara and Bouret, 2012).

We therefore hypothesize that VNS through NE might improve cognitive control on two levels. First, through reduced distractor interference expressed in a smaller congruency effect and second, through learning expressed in a larger SCE. We tested 19 epileptic VNS patients, both during on and off stimulation, while they were executing an arrow flanker task (Eriksen and Eriksen, 1974). We further compare the effect of VNS on cognitive control between clinically determined responder and non-responder VNS patients.

2. Methods

2.1. Participants

Nineteen VNS patients participated in this study; two patients could not complete the study due to fatigue (mean age = 43 years [range, 21–66], 11 female, 15 right-handed). All patients gave written informed consent. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local university hospital ethics committee. A VNS patient is medically considered a responder when there is a monthly seizure frequency reduction of at least 50% compared to before VNS therapy.

Patients were included in the study if they met the following criteria: 1) at least 18 months of treatment with VNS for refractory epilepsy; 2) older than 18 years; 3) full-scale IQ score ≥ 70 on the Wechsler Adult Intelligence Scale, Third Edition. Only patients who were treated with VNS for at least 18 months were included because current reports suggest that VNS efficacy has a tendency to improve up to 18 months after surgery, after which a plateau is usually reached (Boon et al., 2007; Shahwan et al., 2009). Patients were divided into 2 groups depending on their reduction in mean monthly seizure frequency: 10 responders (> 50% reduction) and 9 non-responders (≤ 50% reduction). Mean monthly seizure frequency was defined as the mean seizure frequency during the 3 consecutive months before implantation and before testing. The mean monthly seizure frequency before VNS was not significantly different between both groups (non-responders: $M = 58.6$, $SD = 55.2$ seizures/month; responders: $M = 39.3$, $SD = 48.4$ seizures/month; $t(17) = 0.81$, $p = .43$). Conversely, the mean monthly seizure frequency reduction post-VNS was significantly higher in the group of responders (86.7%) than in the group of non-responders (10.3%) ($t(17) = 9.63$, $p < .001$). Of the two patients who could not complete the study, one was a responder, the other a non-responder.