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Mixed evidence for the potential of non-invasive transcutaneous vagal nerve stimulation to improve the extinction and retention of fear

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ABSTRACT

Extinction memories are fragile and their formation has been proposed to partially rely on vagus nerve activity. We tested whether stimulating the auricular branch of the vagus (transcutaneous VNS; tVNS) accelerates extinction and reduces spontaneous recovery of fear. Forty-two healthy students participated in a 3-day fear conditioning study, where we tested fear acquisition (day 1), fear extinction (day 2) and the retention of the extinction memory (day 3). During extinction, participants were randomly allocated to receive tVNS or sham stimulation concurrently with each CS presentation. During the acquisition and retention phases, all participants received sham stimulation. Indexes of fear included US-expectancy, startle blink EMG and skin conductance responses. Results showed successful acquisition and extinction of fear in all measures. tVNS facilitated the extinction of declarative fear (US expectancy ratings), but did not promote a stronger retention of the declarative extinction memory. No clear effects of tVNS on extinction and retention of extinction were found for the psychophysiological indexes. The present findings provide tentative indications that tVNS could be a promising tool to improve fear extinction and call for larger scale studies to replicate these effects.

1. Introduction

Fear is an evolutionarily adaptive response to actual or potential harm that predisposes the body towards a defensive reaction (Fendt & Fanselow, 1999). The acquisition of fear is strongly dependent on the process of Pavlovian conditioning (Indovina, Robbins, Nunez-Elizalde, Dunn, & Bishop, 2011; Lissek et al., 2005; Mineka & Zinbarg, 2006): When a neutral stimulus (conditioned stimulus, CS) is contingently paired with an inherently aversive stimulus (unconditioned stimulus, US), the CS will start to elicit a learned or conditioned fear response (CR). This Pavlovian conditioning of fear is most often adaptive as it allows an individual to learn from aversive experiences. However, it can also lead to pathological anxiety. For example, in recent years it has become clear that patients with anxiety disorders and stress-related disorders including post-traumatic stress disorder have difficulties extinguishing the learned fear response (for a recent meta-analysis, see Duits et al., 2015). That is, when the CS is no longer followed by a US, anxiety patients show prolonged fear responses in the absence of clear threat. This finding is in line with studies showing that exposure therapy, the treatment of choice for most anxiety and trauma-related disorders (Mark E Bouton, Mineka, & Barlow, 2001; Hofmann, 2007), is only moderately effective (Stewart & Chambless, 2009). Understanding the neurobiological mechanisms behind fear and safety learning is therefore crucial in order to improve the treatment of anxiety and trauma-related disorders.

Knowledge about the neurobiological underpinnings of fear learning is accumulating. During situations of imminent threat, the body initiates a fight-flight-response, consisting of a cascade of bodily reactions that allow appropriate responding to the stressor. Of particular importance to fear learning, the appraisal of danger or threat leads to the release of peripheral epinephrine (Mcgaugh & Roozendaal, 2002), which activates beta-adrenergic receptors on the afferent vagus nerve. When this afferent information reaches the nucleus of the solitary tract, noradrenergic projection neurons in the locus coeruleus (LC) are activated and release norepinephrine (NE) in several cortical and subcortical brain regions that support memory formation (McGaugh, 2002). Due to this increased release

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Abbreviation

tVNS transcutaneous vagus nerve stimulation

of NE, fear memories are more strongly consolidated and subsequently more easily remembered than neutral memories (Cahill & Mcgaugh, 1998).

Meta-analyses have indicated that this system of learning new and emotional memories is thwarted during extinction learning (Duits et al., 2015; Lissek et al., 2005). Experimental studies have found that the consolidation of extinction memory could be enhanced by utilizing the same mechanism through which a fear memory attains its privileged position in memory storage. For example, promoting NE release in cortical and limbic structures through the use of yohimbine, an alpha2-adrenoreceptor, has the potential to facilitate fear extinction (Mueller & Cahill, 2010). Unfortunately, yohimbine increases the release of central NE by increasing peripheral adrenal activity. Therefore, the use of yohimbine in patients is not warranted, as it may increase arousal which may have anxiety-provoking effects in anxiety patients (Cain, Blouin, & Barad, 2004). Especially in patients with panic disorder, increased peripheral arousal during exposure therapy may have iatrogenic effects and strengthen the fear memory instead of establishing an extinction memory.

More recently, stimulation of the vagus nerve (VNS) has been proposed as a non-pharmacological alternative to enhance extinction memory through the increase of noradrenergic transmission (Peña, Engineer, & McIntyre, 2013). Low levels of vagus nerve activity – as measured by vagally-mediated heart rate variability - have been observed in anxiety patients (Chalmers, Quintana, Abbott, & Kemp, 2014; Friedman, 2007). Furthermore, higher levels of vagus nerve activity have been associated with increased ability for safety learning and inhibition of conditioned fear responses (Pappens et al., 2014; Wendt, Neubert, Koenig, Thayer, & Hamm, 2015). Contrary to yohimbine, VNS is unrelated to peripheral adrenergic activity (Hassert, Miyashita, & Williams, 2004) and has repeatedly been found to have anxiolytic effects (e.g., Fang et al., 2015; George et al., 2008; Rong et al., 2016). Electrical stimulation of the vagus nerve leads to activation of the noradrenergic projection neurons in the LC, which causes NE to be released in the brain (Fanselow, 2013; Grimonprez, Raedt, Baeken, Boon, & Vonck, 2015). In line with this, several studies have reported on memory-enhancing effects of VNS in animals as well as in humans (for a review, see Vonck et al., 2014). Specifically, studies in rats have repeatedly underlined the importance of the vagus nerve on the extinction of fear. For instance, cutting the afferent vagal nerve fibers attenuated extinction learning in rats (Klarer et al., 2014). By contrast, stimulating the vagus nerve in rats led to enhanced extinction learning (Alvarez-Dieppa, Griffin, Cavalier, & Mcintyre, 2016; Peña et al., 2014, 2013), but only when VNS was conducted during and not after the extinction phase (Peña et al., 2013). Due to the invasive nature of VNS, research on potential effects of vagus nerve stimulation on fear extinction in humans has been limited.

In the past decade, non-invasive ways of stimulating the vagus nerve in humans have been developed, commercialized and approved for clinical use in epileptic and depressive patients (Ben-Menachem, Revesz, Simon, & Silberstein, 2015). Evidence indicates that implanted VNS and transcutaneous stimulation of the auricular branch of the vagus nerve stimulate similar brain structures (Frangos, Ellrich, & Komisaruk, 2014). In line with this, recent studies have documented a range of effects of tVNS in humans, including an enhancement of associative memory and memory of emotional events (Jacobs, Riphagen, Razat, Wiese, & Sack, 2015). Critically, tVNS has been found to promote inhibitory processes, which might be compromised in anxiety patients, such as inhibitory control (Beste et al., 2016; Sellaro, Leusden, & Colzato, 2015) and – at the neural level – the functional connectivity between the right amygdala and the dorsolateral prefrontal cortex (Liu et al., 2016). We have previously examined the effects of tVNS on fear extinction and retention. These preliminary findings suggested that tVNS accelerates the formation of declarative extinction memories in healthy humans (Burger et al., 2016), although we found no evidence for an enhanced consolidation of the extinction memory, as reflected by the lack of significant differences in explicit fear on the retention test 24 h later. The paradigm that was used failed to elicit differential fear conditioning on psychophysiological indices of fear, and thus we were unable to assess potential effects tVNS may have on psychophysiological fear responses.

The present study therefore aimed to further investigate effects of tVNS during extinction training in healthy humans with another type of paradigm. First, to ensure fear learning, the present study used an electrocutaneous stimulus as US, as opposed to the auditory US used in our previous study. Second, acquisition, extinction, and retention of extinction were tested on three separate days, ensuring sufficient time for both the acquisition and extinction memories to consolidate. Furthermore, in contrast to Burger and colleagues (Burger et al., 2016), we now specifically paired the extinction learning trials with tVNS, which yielded the strongest effects in the animal studies by Peña et al. (2013). Our main hypotheses were that tVNS would accelerate the extinction of both declarative and psychophysiological fear responses. Additionally, we hypothesized that tVNS would increase the consolidation of extinction memories, contrary to what was found in our previous study (Burger et al., 2016) but in line with animal studies on the effects of VNS on fear extinction (Peña et al., 2013).

2. Methods

2.1. Participants

Forty-two healthy students from the University of Leuven (16 men and 26 women; age range: 20–36 years) participated in the experiment.[1] In return they received a financial compensation of 70 euros and a one in three chance to win a cinema ticket after completion of the entire experiment. Participants between the ages of 18 and 50 could participate in this study. Exclusion criteria included self-reported current or past psychiatric, cardiac or neurological disorders, use of psychopharmacology or any medication that affects autonomic nervous functioning (e.g., beta-blockers) and pregnancy.

The study was approved by the Medical Ethical Committee of the University of Leuven. Additionally, this study has been pre-registered at ClinicalTrials.gov under NCT02113306.

[1] The current study was part of a larger study. Halfway through data collection, a second control group was added that included a context shift during day 2, comparable to the tVNS condition. In contrast to the first control condition, participants in this condition received sham stimulation to their right ear on the second day. However, participants in this second control group reported significantly lower US expectancy ratings to the CS+ during the acquisition phase compared to both the tVNS group and the first control group. For this reason, we concluded that the participants in this second control group were not comparable to the participants who were recruited from the beginning of the study. The data of the second control group is not included in this manuscript but can be requested alongside the data for the other two experimental groups from the first author.