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Influencing connectivity and cross-frequency coupling by real-time source localized neurofeedback of the posterior cingulate cortex reduces tinnitus related distress

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ABSTRACT

Background: In this study we are using source localized neurofeedback to moderate tinnitus related distress by influencing neural activity of the target region as well as the connectivity within the default network.
Hypothesis: We hypothesize that up-training alpha and down-training beta and gamma activity in the posterior cingulate cortex has a moderating effect on tinnitus related distress by influencing neural activity of the target region as well as the connectivity within the default network and other functionally connected brain areas.
Methods: Fifty-eight patients with chronic tinnitus were included in the study. Twenty-three tinnitus patients received neurofeedback training of the posterior cingulate cortex with the aim of up-training alpha and down-training beta and gamma activity, while 17 patients underwent training of the lingual gyrus as a control situation. A second control group consisted of 18 tinnitus patients on a waiting list for future tinnitus treatment.
Results: This study revealed that neurofeedback training of the posterior cingulate cortex results in a significant decrease of tinnitus related distress. No significant effect on neural activity of the target region could be obtained. However, functional and effectivity connectivity changes were demonstrated between remote brain regions or functional networks as well as by altering cross frequency coupling of the posterior cingulate cortex.
Conclusion: This suggests that neurofeedback could remove the information, processed in beta and gamma, from the carrier wave, alpha, which transports the high frequency information and influences the salience attributed to the tinnitus sound. Based on the observation that much pathology is the result of an abnormal functional connectivity within and between neural networks various pathologies should be considered eligible candidates for the application of source localized EEG based neurofeedback training.

1. Introduction

Neurofeedback is a brain-computer interface method that makes it possible for users to gain voluntary control of their cortical oscillations by receiving direct feedback from their EEG (Congedo et al., 2004). In other words, humans can learn how to shape their brain electrical activity in a desired direction (Congedo et al., 2004) through operant conditioning (Sterman et al., 1970). Neurofeedback is considered efficacious for ADHD (Micoulaud-Franchi et al., 2014) and medically intractable epilepsy (Tan et al., 2009). In classical neurofeedback, usually only one recording electrode is used, recording electrical activity from widespread cortical areas. This has been successfully used in tinnitus in pilot studies (Dohrmann et al., 2007; Hartmann et al., 2014; Kahlbrock and Weisz, 2008). However, the development of source localized neurofeedback (Congedo et al., 2004; Cannon et al., 2009) permits to

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train specific targets in the brain, such as the anterior cingulate cortex and possibly the posterior cingulate cortex, potentially changing activity in the trained area and connectivity to/from the trained area (Cannon et al., 2009).

The posterior cingulate cortex is the most densely connected brain area (Tomasi and Volkow, 2010), part of the self-referential (Buckner et al., 2008; Svoboda et al., 2006) default mode network (Raichle et al., 2001) and its overall function is postulated to permit adaptation of the self to a changing internal and external environment (Pearson et al., 2011). This requires a predictive capacity, based on memory and related to the self. And indeed the default mode network is involved in remembering the past to predict the future (Schacter et al., 2007). It has 4 subregions, each with a specific function to permit this formidable task (Leech and Sharp, 2014): the precuneus is associated with attention, the ventral posterior cingulate cortex processes information from the internal world, the dorsal posterior cingulate cortex processes information from the external world, and the retrosplenial cortex which is connected to the ant thalamus and (para)hippocampus, is associated with memory processes (Leech and Sharp, 2014). The posterior cingulate cortex is also involved in tinnitus (De Ridder et al., 2011a,b; Maudoux et al., 2012a,b; Moazami-Goudarzi et al., 2010; Schecklmann et al., 2013; Silchenko et al., 2013; Vanneste and De Ridder, 2012a; Vanneste and De Ridder, 2012b; Vanneste and De Ridder, 2015a; Vanneste et al., 2012; Vanneste et al., 2010a; Weisz et al., 2014) and especially in tinnitus distress (De Ridder et al., 2011a,b; Maudoux et al., 2012a,b; Schecklmann et al., 2013; Silchenko et al., 2013; Vanneste and De Ridder, 2012a; Vanneste and De Ridder, 2012b; Vanneste and De Ridder, 2015a; Vanneste et al., 2012; Vanneste et al., 2010a), in other words, in how the self-adapts to an internally generated sound that is perceived as coming from the external world (Cannon et al., 2009).

Tinnitus, i.e. the perception of a sound in the absence of an external sound source, has been considered as an emergent property of multiple parallel networks, whereas at least two distinct neural networks have been involved, underpinning tinnitus related loudness and distress (De Ridder et al., 2011a,b). Tinnitus is proposed to be a filling-in mechanism of reduced auditory input in order to reduce auditory sensory uncertainty (De Ridder et al., 2014). The loudness and distress networks intercommunicate only in distressed tinnitus patients via a specific and discrete functional connection, i.e. the connection between the parahippocampal area and the subgenual anterior cingulate cortex/ventromedial prefrontal cortex (Vanneste et al., 2013). The posterior cingulate cortex is not only a major hub of the default network but is as well involved in the tinnitus related distress network, in which distressed tinnitus patients have a decrease in alpha activity (Vanneste et al., 2010a, 2013), a frequency range that normally correlates positively with activity in the default network (Mantini et al., 2007). However, reduction of tinnitus related distress has been correlated with increased synchronization of alpha activity in the posterior cingulate cortex combined with decreased beta and gamma activity within the precuneus/posterior cingulate cortex (Vanneste and De Ridder, 2012b). Additionally, desynchronization of alpha activity seems to be related to cognitive processing (Nunez et al., 2001), which might suggest that distressed tinnitus patients are continuously actively engaged in processing the tinnitus sound resulting in a constant state of attentional processing. Based on these observations, we hypothesize that up-training alpha and down-training beta and gamma activity in the posterior cingulate cortex has a moderating effect on tinnitus related distress by influencing neural activity of the target region as well as the connectivity within the default network and other functionally connected brain areas.

2. Methodology

2.1. Subjects

Fifty-eight patients with chronic tinnitus were included in the study from the Tinnitus Research Initiative (TRI) clinic, Antwerp, Belgium. The mean age of the patients was 45.36 years ($Sd = 9.54$) and the mean tinnitus duration was 3.56 years ($Sd = 4.23$). Of these 58 patients, 23 tinnitus patients received NF training of the posterior cingulate cortex with the aim of up-training alpha and down-training beta and gamma activity, while 17 patients underwent training of the lingual gyrus as a control situation. The lingual gyrus is adjacent to the posterior cingulate cortex and the parahippocampal gyrus, but not involved in tinnitus distress processing. Its main function is related to visual rather than auditory processing. A second control group consisted of 18 tinnitus patients on a waiting list for future tinnitus treatment.

Individuals with pulsatile tinnitus, Ménière disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, and individuals being treated for mental disorders were not included in the study in order to obtain a homogeneous sample. All patients included for this study first underwent a complete audiological, ENT, and neurological investigation. In addition, several technical investigations were performed, including MRI of the brain. Collection of the data was under approval of IRB UZA OGA85. All patients gave an informed consent.

2.2. Healthy control group

Group age and gender matched EEG data of a healthy control group ($N = 22$; $M = 45.2$ years; $Sd = 10.02$) was collected. None of these subjects were known to suffer from tinnitus. Exclusion criteria were known psychiatric or neurological illness, psychiatric history or drug/alcohol abuse, history of head injury (with loss of consciousness) or seizures, headache, or physical disability.

2.3. Questionnaires

All patients filled out a numeric rating scale (NRS) before and after the NF training measuring tinnitus loudness ('How loud do you perceive your tinnitus?': 0 = no tinnitus and 10 = as loud as imaginable). Moreover, to assess tinnitus severity all patients filled in the validated Dutch version of the Tinnitus Questionnaire (TQ) (Meeus et al., 2007; Vanneste et al., 2010b), originally published by Goebel and Hiller (1994), and shown to be a reliable measure for tinnitus-related distress (Vanneste et al., 2010b). The global TQ score can be computed to measure the general level of psychological and psychosomatic distress, with a further subdivision made to measure emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints. A 3-point scale is given for all 52 items, ranging from "true" (2 points) to "partly true" (1 point) and "not true" (0 points). The total score (from 0 to 84) was computed according to standard criteria published in previous work (Hiller and Goebel, 1992; Hiller et al., 1994; Meeus et al., 2007). Based on the total score on the TQ, participants were assigned to a distress category: slight (0–30 points; grade 1), moderate (31–46; grade 2), severe (47–59; grade 3), and very severe (60–84; grade 4). Furthermore, Goebel and Hiller (1994) stated that grade 4 tinnitus patients are psychologically decompensated, indicating that patients categorized into this group cannot cope with their tinnitus.

2.4. Neurofeedback training

The neurofeedback training was performed using Brain Tuner

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