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Bursts of transcranial electrical stimulation increase arousal in a continuous performance test

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ABSTRACT

Arousal reflects a state of generalised physiological activation, and its key role in cognition and behaviour has been extensively described. The regulation of arousal is controlled by specific nuclei located in the brainstem that contain widely distributed projections to the cortex and form the arousal systems. In humans, arousal has been commonly studied and modulated through behavioural paradigms, whereas in animals, direct electrical stimulation has been used to confirm the important role of these widely distributed structures. Recent evidence suggests that it might be possible to use transcranial electrical stimulation (tES) to non-invasively induce currents in the brainstem regions of the brain. Therefore, we hypothesise that, using a specific electrode arrangement, it might be possible to employ tES to stimulate subcortical–cortical neuromodulatory networks, inducing modulation of general arousal. The aim of the present study was to determine if it is possible to increase arousal during a discriminative reaction times (RTs) task, through the application of tES, to improve the subjects' performance.

We developed 3 experiments: Experiment 1 validated the behavioural task, which was an adapted version of the continuous performance test. Experiment 2 aimed to show the task sensitivity to the level of activation. The results confirmed that the task was sensitive enough to reveal modulations of arousal. In Experiment 3, we applied bursts of tES concurrent with the onset of the relevant stimuli of the task to increase the physiological phasic activation of arousal. The skin conductance response was recorded during the experiment in addition to the RTs. The results showed a reduction of RTs and a concurrent increase in skin conductance during the real stimulation condition, which is consistent with a general increase in arousal. In all, these data support the effectiveness of bursts of tES in modulating arousal.

1. Introduction

Arousal reflects a state of generalised physiological and psychological activation that is closely related to a variety of phenomena such as attention, motivation, anxiety and sleep (Robbins and Everitt, 1995a; Sara, 2009). Regulation of arousal and sleep–wake transitions is achieved by several nuclei that are widely distributed in the brainstem. These nuclei have neuromodulatory functions and various projections to the cortical and subcortical structures. Instead of carrying detailed sensory information, they modulate large groups of post-synaptic neurons (e.g., neurons of the cerebral cortex, thalamus, and spinal cord) by increasing or decreasing their excitability. One of these neuromodulatory nuclei is the locus coeruleus (LC), which has historically been related to the regulation of arousal (Aston-Jones and Cohen, 2005; Aston-Jones et al., 1999; Sara and Bouret, 2012). Recordings from primate LC neurons during several tasks have shown two distinguishable functioning modes (Clayton et al., 2004; Usher et al., 1999). In the phasic mode, bursts of LC activity are observed during the processing of motivationally relevant stimuli, leading to the release of noradrenaline (NA) in the hippocampus, neocortex, and many other projection areas. This state of activation has been proposed to facilitate reward-seeking behaviours and help optimise task performance (exploitative behaviour). Conversely, in the tonic mode, the basic activity of the LC is increased, while the bursts of phasic activity are absent. During the tonic mode, subjects tend to explore the context, searching for other motivationally relevant stimuli, resulting in a more distractible behaviour (explorative behaviour) that might decrease task performance (Aston-Jones and Cohen, 2005).

Several studies on humans and animals have reported the key role of arousal in cognition (Berridge and Waterhouse, 2003; Brown et al., 2014). In humans, arousal is commonly modulated through emotional stimuli (Sutherland and Mather, 2012; Dew

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et al., 2014), warning cues (Hackley, 2009) and conflict paradigms (Brown et al., 2014), inducing an improvement of the behavioural performance as arousal increased. It has been demonstrated that an arousing stimulus can amplify the effect of saliency in short-term memory (Sutherland and Mather, 2012) and even enhance visual perception (Zeelenberg and Bocanegra, 2010) and memory retrieval (Mather and Sutherland, 2011). The importance of arousal in cognition has also received empirical support from studies regarding rehabilitative interventions in brain injured patients (Levine et al., 2011; Manly et al., 2002) and children with attention-deficit hyperactivity disorder (O'Connell et al., 2006). These studies showed that alerting cues improve executive functions.

In animals, the role of arousal has been widely studied using electrical stimulation applied directly to the LC. Activation of the LC during a demanding task, with the consequent release of NA to the cortex, has been demonstrated to have an impact on the focus of attention and processing of the stimuli (Clayton et al., 2004; Sara, 2009). In a recent study, Lim et al. (2010) showed that electrical stimulation of the LC in rats can promote long-term potentiation of hippocampal-frontal synapses, which are involved in long-term offline memory consolidation. Further evidence has shown that the release of NA by electrical stimulation of the LC in rats facilitates retrieval of the correct directions in a maze (Sara and Devauges, 1988).

In recent years, electrical stimulation has been widely applied to humans due to its ability to modulate cortical excitability in a non-invasive manner (Nitsche et al., 2008; Priori, 2003). Transcranial electrical stimulation (tES) involves the application of weak electrical currents by a pair of electrodes applied directly to the head, and has been used both to modify behavioural performance in a wide range of cognitive tasks (e.g., Jacobson et al., 2012; Vallar and Bolognini, 2011; Brignani et al., 2013; Pellicciari et al., 2013) and in the treatment of neurological disorders such as chronic pain, Parkinson's disease and Alzheimer's disease (e.g., Boggio et al., 200·9, 2012; Ferrucci et al., 2008). tES generates an electrical field that modulates neuronal activity according to the modality of the application, which can be direct (transcranial direct current stimulation), alternating (transcranial alternating current stimulation) or random noise (transcranial random noise stimulation). Another type of non-invasive electrical stimulation consists of cranial electrotherapy stimulation (CES). This technique has been in clinical use for the last fifty years for the treatment of many emotional and physical disorders such as depression, anxiety and insomnia. CES provides small pulses of electric current across the head of the patients at different frequencies, usually between 0.5 Hz and 100 Hz (Kirsch and Nichols, 2013; Smith, 2006), with specific electrode arrangements. Although CES has been regulated by the U.S. Food and Drug Administration since 1977, its mechanism of action is not clear, but it may affect the release of neurotransmitters across the cortex. This explanation is consistent with evidence suggesting a broad diffusion of the current under the stimulation sites, which could affect several distributed neuromodulatory systems. Evidence for a generalised effect of CES was reported in studies during the first half of the last century (Hayes, 1950; Smitt and Wegener, 1944), and has received further confirmation from more recent investigations. Modelling studies, based on computational simulations of the brain (Bikson et al., 2012; Laakso and Hirata, 2013; Sadleir et al., 2010; Wagner et al., 2014), as well as studies using neuroimaging techniques (Alon et al., 2011; Antal et al., 2011; Lang et al., 2005; Lindenberg et al., 2013), have reported that, according to the arrangement used, there is extensive diffusion of the current that is not limited to the areas under the stimulation electrodes; CES also influences other structures (e.g., the brainstem).

Therefore, we hypothesise that the application of tES with a certain electrode arrangement should stimulate neuromodulatory cortical and subcortical networks, inducing an exogenous modulation of arousal. The aim of this study was to use tES to increase the arousal of participants during a discriminative reaction time task to improve performance. We predict that the application of bursts of tES concurrent with the presentation of behaviourally relevant stimuli could increase the phasic arousal response.

2. Experiments 1 and 2: behavioural task validation

The first step of our research was to verify if the paradigm we chose was sensitive enough to reveal arousal modulations. Therefore, we developed two experiments using an adapted version of the continuous performance test (CPT), which has been widely used in many studies to measure sustained and selective attention (Conners et al., 2003; Riccio et al., 2002; van den Bosch et al., 1996). During the task, participants had to press response buttons for target digits that appeared after a warning digit. Because the warning digit forces participants to prepare for the response, an endogenous increase of arousal during the warning-target interval is expected. To further increase this level of arousal, we used bursts of white noise presented to the participants through headphones at a volume of 90 db. We chose to use this type of arousing auditory stimulus because we wanted to induce a nonspecific activation concurrent to the preparation of the response, and we were not interested in the processing of the emotional connotation of the stimulus.

We evaluated the response speed as a measure of the behavioural performance because a reduction in reaction time (RT) has been demonstrated in conditions of increased arousal, indicating a performance improvement (Bagherli et al., 2011; VaezMousavi et al., 2009; VaezMousavi et al., 2007a). In order to get an indication about the level of activation experienced by the participants, we recorded a subjective report before the experiment. Given (i) the lack of a specific questionnaire for the evaluation of the arousal state and (ii) the strict relation reported in literature between anxiety sensitivity and somatic arousal sensations (Pané-Farré et al., 2014; VaezMousavi and Osanlu, 2011), we administered the State-Trait Anxiety Inventory (STAI-Y) (Spielberger et al., 1983) to all the participants. As reported by Eysenck (1967), subjects with high levels of anxiety are more aroused than those with low levels of anxiety. The activity of NA neurons in the LC is facilitated during stressful conditions, with a strict relation to increased anxiety (Mizuki et al.,1997; Robbins and Everitt, 1995b). Several studies, in addition, reported anxiety disorders as characterized by elevated autonomic arousal driven by NA activity. This system itself has been shown to mediate both anxiety, vigilance and attention (Aston-Jones et al., 1991, 1994; Berridge and Waterhouse, 2003; Grisham et al., 2015).

2.1. Experiment 1

In the Experiment 1 we tested whether bursts of white noise combined with a warning stimulus could increase the arousal of the participants, resulting in an improvement in performance compared to a condition in which the warning stimulus was presented without any white noise.

2.1.1. Materials and methods

2.1.1.1. Participants. Twenty-three healthy volunteers participated in Experiment 1 (18 females, mean age=27.5 years; SD=2.9). Two of them were excluded from the analyses due to a lower accuracy or to a higher slowness compared to the overall mean of the participants (see Section 2.1.1.3). All participants had normal or corrected-to-normal visual acuity and were right handed according to the Edinburgh handedness inventory test (Oldfield, 1971).

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