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The norepinephrine system and its relevance for multi-component behavior

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ABSTRACT

The ability to execute several actions in a specific temporal order to achieve an overarching goal, a process often termed action cascading or multi-component behavior, is essential for everyday life requirements. We are only at the beginning to understand the neurobiological mechanisms important for these cognitive processes. However, it is likely that the locus coeruleus-norepinephrine (LC-NE) system may be of importance. In the current study we examine the relevance of the LC-NE system for action cascading processes using a system neurophysiological approach combining high-density EEG recordings and source localization to analyze event-related potentials (ERPs) with recordings of pupil diameter as a proximate of LC-NE system activity. N=25 healthy participants performed an action cascading stop-change paradigm. Integrating ERPs and pupil diameter using Pearson correlations, the results show that the LC-NE system is important for processes related to multi-component behavior. However, the LC-NE system does not seem to be important during the time period of response selection processes during multi-component behavior (reflected in the P3) as well as during perceptual and attentional selection (P1 and N1 ERPs). Rather, it seems that the neurophysiological processes in the fore period of a possibly upcoming imperative stimulus to initiate multi-component behavior are correlated with the LC-NE system. It seems that the LC-NE system facilitates responses to task-relevant processes and supports task-related decision and response selection processes by preparing cognitive control processes in case these are required during multi-component behavior rather than modulating these processes once they are operating.

1. Introduction

To cope with most everyday tasks, one has to execute several actions in a specific temporal order to achieve an overarching multi-component goal. Doing so, we are quite often required to interrupt an ongoing action and turn to an alternative action. During such multi-component behavior we heavily depend on action cascading processes, which are defined as the ability to generate, process, and execute separate task goals and responses in an expedient temporal order to produce an efficient goal-directed multi-component behavior (Dippel and Beste, 2015; Duncan, 2010; Mückschel et al., 2015, 2014, Stock et al., 2015, 2014). These processes have been shown to differ in their demands on cognitive control and response selection processes, depending on whether stimuli signaling to execute one specific behavior are presented simultaneously, or with a temporal gap in between. This makes it possible to finish one behavioral subprocess in the chain of actions before executing another one.

A number of neurobiological factors have already been shown to modulate these processes. For example, using transcranial vagus nerve stimulation (tVNS), known to modulate the GABAergic and the norepinephrine (NE) system (Raedt et al., 2011; Van Leusden et al., 2015), it has been shown that action cascading processes become faster (Steenbergen et al., 2015). Both, the GABAergic and the NE system are therefore likely to play a role, but from the data by Steenbergen et al. (2015), it cannot be concluded which of the two modulated systems (i.e. GABA or NE) are central to modulations in action cascading. While the relevance of the GABAergic system for these processes has been underlined using magnetic resonance spectroscopy (Yildiz et al., 2014) there is no knowledge about the role of the NE system. The NE system may be of particular relevance since it has been suggested that one property of the locus coeruleus-NE function (LC-NE) is to modulate task-related decision or selection processes (for review: Aston-Jones and Cohen, 2005) with phasic LC-NE responses probably facilitating responses to task-relevant processes (Aston-Jones and Cohen, 2005; Nieuwenhuis et al., 2005). Exactly such processes are important for action cascading and multi-component behavior (Mückschel et al., 2014), which makes it likely that phasic LC-NE responses are related to this important executive control function.

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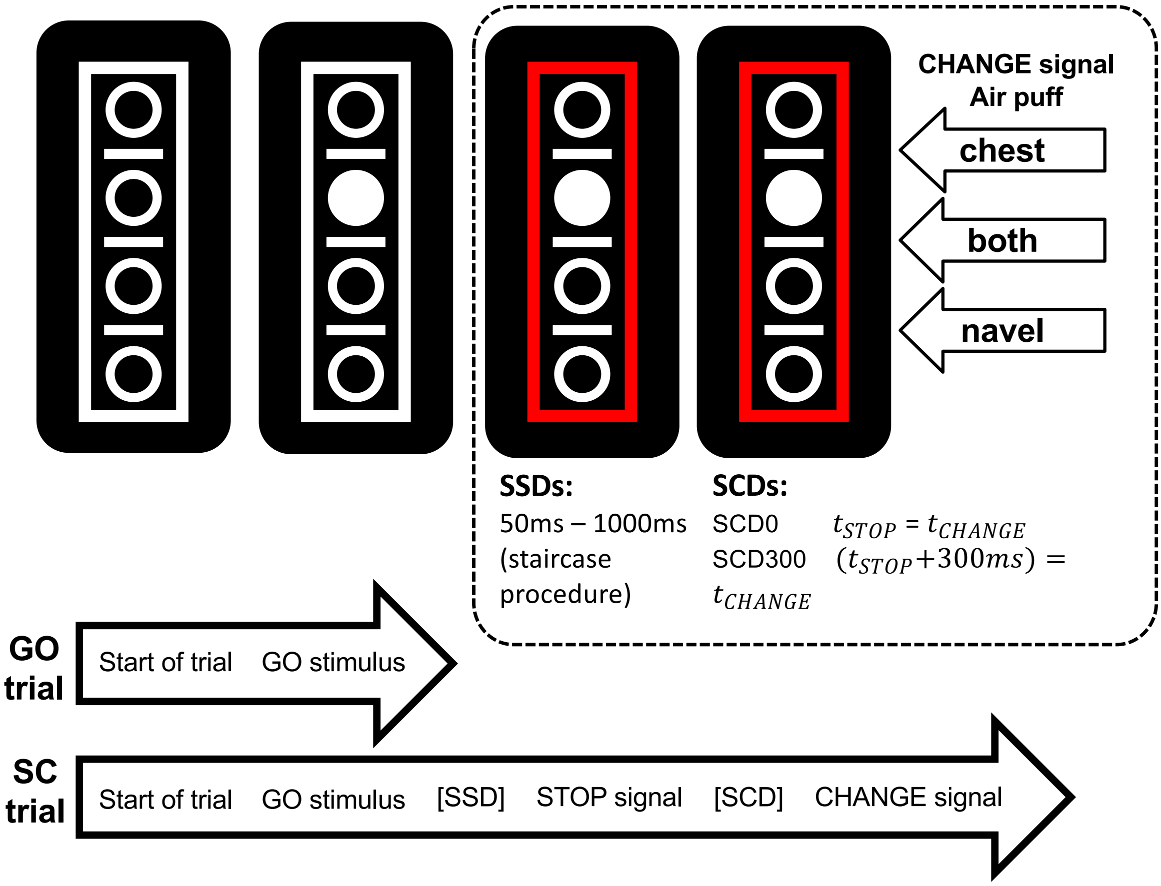

Fig. 1. Illustration of the Stop-Change task used in this study. GO trials end after the first response to the GO stimulus. SC trials end after the first response to the CHANGE signal. The stop-signal delay (SSD) between the onset of GO stimulus and STOP signal was adjusted using a staircase procedure. The CHANGE signal was presented after a stop-change delay (SCD) of either 0 ms or 300 ms. Different locations and combinations of air puffs were associated with one of the three reference lines.

The goal of the current study is to investigate the relevance of the LC-NE system for multi-component behavior using a Stop-Change task. This goal is pursued in a system neurophysiological approach using high-density EEG recordings to analyze event-related potentials (ERPs) and their related neuronal sources combined with recordings of pupil diameter. The pupil diameter has been suggested not only to be modulated by tonic, but also by phasic LC-NE activity (Hou et al., 2005; Murphy et al., 2011). Therefore, recordings of the pupil diameter are frequently used when interested in LC-NE functions in relation to cognitive functions in humans (Gilzenrat et al., 2010; Hong et al., 2014; Jepma and Nieuwenhuis, 2010; Murphy et al., 2011). Opposed to a pharmacological manipulation of the NE system, the continuous recording of the pupil diameter in combination with ERPs offers the advantage to examine which cognitive subprocess and at which precise time point during information processing in a given task the NE system is of importance. The latter aspect is of particular relevance to examine a possible role of phasic LC-NE responses for dissociable subprocesses during multi-component behavior.

On a neurophysiological (EEG) level, the P3 ERP has frequently been suggested to reflect decision processes between stimulus evaluation and motor responding, i.e. action selection processes (e.g. Twomey et al., 2015; Verleger et al., 2015). In line with this, response selection mechanisms during action cascading have been shown to be reflected by P3 ERP amplitude modulations having their source in anterior cingulate (ACC), inferior parietal and inferior frontal cortices (Beste et al., 2014a; Dippel and Beste, 2015; Stock et al., 2015). Especially ACC regions show stronger activation in situations when response selection mechanisms can operate in a suboptimal (parallel) fashion, i.e. when multiple response options are handled at the same time (e.g. Mückschel et al., 2014). These situations are linked to higher P3 amplitudes during multi-component behavior. The reason is that the P3 likely reflects inhibition processes and changing processes. This is especially the case when people handle response options at the same time (Dippel and Beste, 2015). As has been shown before (Beste et al., 2014b), the more participants attempt to simultaneously process the “stop-goal” and the “change-goal” in a Stop-Change task used to examined multi-component behavior, the stronger is the interference between these goals at a strategic response selection bottleneck (Verbruggen et al., 2008). Inhibitory control processes to manage the stopping of a response are likely to be intensified due to this strong interference. Such an intensification of response inhibition efforts has frequently been shown to be related to higher P3 amplitudes (Huster et al., 2013a).

Importantly, it has been suggested that the P3 is an electrophysiological correlate of the LC phasic NE response (Murphy et al., 2011; Nieuwenhuis et al., 2005). We therefore hypothesize that especially these response selection processes (reflected by the P3) related to medial frontal cortices are correlated with LC-NE responses. Higher NE concentrations, as reflected by a larger pupil diameter (Hou et al., 2005; Phillips et al., 2000), are supposed to be related to more efficient response selection processes during multi-component behavior. However, the “LC-P3” theory has more recently been modified (Warren et al., 2011; Warren and Holroyd, 2012). According to these modifications LC bursts impact cortical activity earlier than during the time frame of the P3, i.e. ~250 ms post stimulus, and it is the LC refractory period that coincides with the P3 generation. An alternative hypothesis may therefore be that the LC-NE system is specifically correlated with neurophysiological processes prior the P3. Previous studies suggest that aside from response selection processes, also perceptual gating and attentional selection mechanisms, reflected by