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Towards response success prediction: An integrative approach using high-resolution fMRI and autonomic indices

Stefanie Köhler, Andy Schumann, Feliberto de la Cruz, Gerd Wagner, Karl-Jürgen Bär*

Psychiatric Brain and Body Research Group, Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany

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ABSTRACT

Brainstem and midbrain nuclei are closely linked to effective cognitive performance and autonomic function. In the present study, we aimed to investigate indices of successful and unsuccessful response inhibition paying particular attention to the interplay between locus coeruleus (LC), ventral tegmental area (VTA)/substantia nigra (SN) and, most importantly, peripheral markers. We aimed to get insight in the predictive value of neural and physiological signals in response inhibition.

A total of 35 healthy controls were recruited from the local community and a typical task of behavioral response inhibition (Go/No-Go paradigm) was applied. We used high-resolution fMRI, advanced brainstem analyses and specifically corrected for respiratory signal and cardiac noise.

Our main results characterize specific neural activation patterns during successful and unsuccessful response inhibition especially comprising the anterior cingulate as well as the medial and lateral prefrontal cortex. A significant activation of the dopaminergic nuclei (VTA/SN) was found during error processing, but not during response inhibition. Most remarkably, specific neural activation patterns (i.e., dorsal anterior cingulate cortex) as well as accompanying autonomic indices (i.e., skin conductance response (SCR)) were identified to hold predictive information on an individual's performance.

In summary, the importance of the VTA/SN during error processing was shown. Furthermore, autonomic indices and specific neural activation patterns may contain valuable information to predict task performance.

1. Introduction

Spontaneous and rash behavior is characteristic for impulsive individuals and might frequently result in behavioral failures. Some psychiatric disorders (e.g., attention deficit hyperactivity disorder; Brewer and Potenza, 2008) are characterized by elevated impulsivity or diminished behavioral flexibility, which can result in adverse consequences for both the individual itself and the social environment. It is assumed that impulsivity might arise due to deficient inhibitory processes (Bari and Robbins, 2013). In order to improve the psychopharmacological as well as psychotherapeutic support regarding patients suffering from disorders associated with response inhibition deficits, a comprehensive understanding of its mechanisms is indispensable.

Inhibitory control can be subdivided into a cognitive and behavioral/motor domain (Bari and Robbins, 2013). In a recent study of our group (Köhler et al., 2016), we analyzed the former and showed the functional integration of the noradrenaline (NA) producing locus coeruleus (LC) and dopaminergic (DA) nuclei, i.e., the ventral tegmental area (VTA) and substantia nigra (SN), in the cognitive control network in humans. In our present investigation, we aimed to study the behavioral/motor domain of cognitive control (i.e., response inhibition) and its neural correlates. A central component of this domain is action restraint, which represents the inhibition of a pre-potent response. Therefore, we aim to show whether the cognitive control network is activated during response inhibition integrating the LC and VTA/SN in the analysis. Differences in network composition depending on, for instance, cognitive domain and type of task are feasible. A typical task to measure the ability to inhibit a pre-potent response is the Go/No-Go paradigm (Bari and Robbins, 2013), in which subjects face categorical decisions requiring a response to the “Go” or to withhold a response to the “No-Go” type.

A successful inhibition of pre-potent motor responses (No-Go trials) depends on fronto-striatal loops including the inferior frontal gyrus, the (pre-) supplementary motor area (SMA) and the striatum (Alexander and Crutcher, 1990; Aron and Poldrack, 2006; Jentsch and Taylor, 1999; Simmonds et al., 2008). Deficits in the dorsomedial prefrontal cortex (DMPFC) were found to be responsible for impaired

* Correspondence to: Department of Psychiatry and Psychotherapy, University Hospital Jena, Philosophenweg 3, 07743 Jena, Germany.
E-mail address: Karl-Juergen.Baer@med.uni-jena.de (K.-J. Bär).

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performances in Go/No-Go tasks (Godefroy et al., 1996). Patients with lesions including the (pre-)SMA and subdivisions of the anterior cingulate cortex (ACC) showed prolonged reaction times and increased error-rates (Picton et al., 2007; Stuss et al., 2002).

In our previous study, we were unable to study response failure and the possible involvement and predictive value of the LC and VTA/SN in error processing due to a very low number of error trials (Köhler et al., 2016). Thus, the activated whole-brain network during error processing as well as the integration of the LC and VTA/SN needs further clarification.

Error processing is a fundamental cognitive function for adaptive behavior (Lim et al., 2015). When performance errors occur, there is an increased need for behavioral monitoring and cognitive control (Botvinick et al., 2001; Cohen et al., 2000). Failures of response inhibition in No-Go trials usually result in behavioral adaption that can be observed immediately in terms of response slowing in following Go-trials. The brain's error processing network comprises the DMPFC, ACC and SMA (Garavan et al., 2002; van Noordt and Segalowitz, 2012). The error-related brain potential (ERP) induced by incorrect behavioral responses (Gehring et al., 1993; Gehring et al., 2000) was often linked to the ACC (Agam et al., 2014; Miltner et al., 1997; Miltner et al., 2003). The dorsal ACC (dACC) was also associated with attentional and performance monitoring (Shenhav et al., 2016). Error commission is also linked to significant autonomic responses that might facilitate a redirection of attentional focus and performance adjustment (Bechara et al., 1997). The dACC seems to act as interface between cognitive, behavioral and autonomic regulation systems during of error processing (Critchley et al., 2005).

Human and non-human studies have indicated the importance of the dopaminergic system for inhibitory control. The main dopamine–-producing regions VTA/SN are located in the midbrain. Both regions have strong projections to the prefrontal cortex (PFC), the ACC and to the striatum respectively, referred to as mesocortical and nigrostriatal dopaminergic pathways. Goschke and Bolte (2014) proposed that the nigrostriatal pathway modulates cognitive/behavioral control by integrating flexible and stimulus-dependent behavioral tendencies, mainly in the striatum. Goal persistence is modulated by the mesocortical pathway. The dopaminergic neurotransmitter system seems to modulate motor readiness for both response inhibition and activation (Bari et al., 2009). Moreover, dopamine was suggested to be an important neurotransmitter in error processing (Bari and Robbins, 2013; Nandam et al., 2013) and was implicated to impact on the autonomic nervous system (ANS) (Kur'yanova et al., 2017).

The locus coeruleus (LC) is a brainstem structure containing noradrenaline producing neurons. In their review, Aston-Jones and Cohen (2005) emphasized the specific role of the LC in cognitive flexibility. The authors proposed that enhanced LC activity produces a temporally specific release of noradrenaline, which increases the gain of specific task-associated cortical networks and optimizes task appropriate behavior. Besides, the noradrenergic neurotransmitter system seems to be critically involved in inhibiting an already initiated response (Eagle et al., 2008; Robbins and Arnsten, 2009). Thus, a decisive role of the dopaminergic and noradrenergic neurotransmitter systems in successful and unsuccessful response inhibition can be assumed (Claassen et al., 2017; Eagle et al., 2007; Kohno et al., 2016).

The brainstem, as a relay and processing station between the spinal cord, cerebellum and neocortex, contains vital nodes of various functional systems in the central nervous system (CNS) including the autonomic nervous system (ANS). The ANS regulates, for instance, the respiratory, cardiac, vasomotor, and endocrine system to adapt behavior to motor, emotional or cognitive challenges (Critchley et al., 2005; Thayer and Lane, 2000). A growing number of studies have investigated the role of different cortical and subcortical brain regions involved in autonomic control. Important brain regions associated with ANS regulation are the ACC, insula, amygdala, SMA, prefrontal cortices and the midbrain (i.e., VTA) (Beissner et al., 2013).

To gain a more comprehensive understanding of response inhibitory mechanisms, we aimed to combine information from relevant systems (e.g., CNS, ANS) involved (Critchley, 2009; Critchley et al., 2005). Some studies already suggested a close interaction between the peripheral ANS and the CNS in response inhibition and error processing (Critchley et al., 2003; Hajcak et al., 2003; Hofmann et al., 2009; Zhang et al., 2012, 2015). For instance, previous research showed enhanced skin conductance responses (SCRs) to errors in impulsive individuals (Zhang et al., 2012, 2015). Hajcak et al. (2003) applied electroencephalography and a modified Stroop task and found a fronto-centrally negative deflection in the ERP signal as well as an elevation in SCR in error trials. SCR is an important autonomic measure of psychophysiology research since it reflects sympathetic neural responses independently of direct parasympathetic control. SCR is suggested to be closely related to dACC activity (Critchley et al., 2001; Nagai et al., 2004; Zhang et al., 2014) and is used as an indirect measure of cognitive effort. For instance, healthy subjects were found to show increases in SCR prior decision making (Bechara et al., 1997) and the magnitude of ACC activity strongly reflected the degree of anticipatory arousal indexed by SCR (Critchley et al., 2001). Mehler et al. (2009) reported that SCR changes indicate cognitive workload already before the appearance of a clear decline in performance. Moreover, Zhang et al. (2012) applied a Stop-Signal Task and found that fluctuations in SCR during Go trials which followed another Go trial are driven by participants' effort in negotiating between speed and accuracy. In contrast, changes in SCR during trials following a Stop signal are in response to an antecedent response conflict. Thus, there is some evidence that the physiological state might influence successful response inhibition, behavioral monitoring and, remarkably, might already hold predictive information for performance accuracy.

In order to improve our understanding of human behavior and associated dysfunctions, we need to acquire a comprehensive understanding of the interplay between peripheral ANS and CNS in response inhibition focusing on the definite involvement of the dopaminergic and noradrenergic neurotransmitter systems. Here, we used high-resolution functional magnetic resonance imaging (fMRI) during a Go/No-Go task and an MRI-compatible multi-channel physiological recording system to answer the following questions: First, we aimed to identify the neural correlates of successful response inhibition in the Go/No-Go task. Based on our previous study (Köhler et al., 2016) and fMRI studies on response inhibition, we hypothesized increased BOLD activations in the cognitive control network accompanied by increased activation in dopaminergic (VTA/SN) and noradrenergic (LC) centers. Second, we aimed to analyze neural correlates of unsuccessful response inhibition. Based on findings regarding error processing (Shenhav et al., 2016), we assumed increased activation in the dACC and VTA/SN. Further, we want to explore the relationship between these structures and response monitoring, e. g. post-error slowing. Third, we focused on SCR to analyze correct and failed inhibitory responses. In particular, a larger SCR during failed compared to correct No-Go trials was assumed. Fourth, we wanted to get further insight in the predictive value of physiological and neural signals in response inhibition. We hypothesized that significant changes in SCR and neural activation (e.g., dACC) occur immediately before successful and unsuccessful response inhibition.

2. Materials and methods

2.1. Subjects

A total of 35 healthy controls were recruited from the local community. Two subjects were excluded from the final analysis because they reported forgotten task instructions. Thus, the final sample comprised 33 subjects (age M = 26.8 years; SD = 5.2 years; range: 20–40 years; 17 females). Individuals with past or current drug use, sleeping problems, excessive training, internistic peculiarities, neurological or