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Research report

On the role of serotonin and effort in voluntary attention: Evidence of genetic variation in N1 modulation

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ABSTRACT

Ascending serotonergic projections from the raphe nuclei to frontal brain areas and the dense distribution of receptor and transporter sites in prefrontal and sensory regions support the idea that serotonin exerts influence on cognitive functioning. Indeed, growing evidence suggests serotonin to be an important factor in learning and memory; however, its precise role in executive processes particularly in voluntary attention is less clear. Event-related EEG studies showed the N1 potential to predict top-down attention allocation and implicated the auditory N1 in central serotonergic activity. Dipole analyses and single-trial coupling of EEG and fMRI revealed N1 sources in the primary auditory cortex and in the anterior cingulate. In the present study, amplitude variation of the event-related N1 potential was investigated on 72 healthy subjects while performing an auditory novelty oddball paradigm to tap top-down and bottom-up attention allocation. Possible serotonergic effects on voluntary attention were analyzed using allele variants of a functional polymorphism (5-HTTLPR) of the gene encoding the serotonin transporter, a key regulator of serotonergic neurotransmission. Because mental effort has been related to top-down attention and N1 modulation, a measure of stable individual differences in cognitive effort was included. The main result was a strong interaction of 5-HTTLPR and cognitive effort on target N1 amplitude. Greater target-related attention allocation was evident in those carriers of the 5-HTTLPR s-allele who described themselves as being more engaged in effortful processing. We suggest that the observed interaction mirrors the interplay between effort-mediated top-down attention by the ACC and serotonergic adjustment on attentional systems.

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1. Introduction

Serotonergic (5-HT) neurotransmission is a major factor in regulating mood and emotion and is considered to be involved in the pathogenesis of several neuropsychiatric disorders. During the last decades, predominantly the relationship between central 5-HT activity and affective disorders has become an extensive focus of research, and indeed, accumulated pharmacological and genetic evidence has underlined the pivotal role of 5-HT alterations in the pathophysiology of depression and anxiety [31,40]. However, fostered by evidence of ascending 5-HT projections from the raphe nuclei to prefrontal brain areas [29], and of the dense distribution of 5-HT receptor and transporter sites in parts of prefrontal areas and sensory cortices (e.g. [58]), the role of 5-HT has been increasingly discussed in relation to cognitive and sensory functioning.

Growing evidence suggests a role of 5-HT in cognitive processes such as learning and memory (e.g. [33]) and executive functioning (e.g. [24]). In fact, acute tryptophan depletion (ATD) which transiently reduces central 5-HT availability, has been shown to impair long-term memory [43] as well as decision making and reversal learning (e.g. [15]), whereas working memory and planning are largely unaffected [38,43] or even improved by ATD [25,53]. Moreover, ATD has been reported to enhance focused attention during dichotic listening and Stroop performance [7], which is discussed as an outcome of reduced inhibition of 5-HT on monaminergic and acetylcholinergic neurotransmission involved in attentional processes [48,53]. Using the event-related potential (ERP) technique, Ahveninen et al. [1] showed that a decreased level of central 5-HT after ATD alters attentional reorienting and, in the light of the primarily inhibitory effects of 5-HT, may improve attentional resource allocation to target events.

Evidence from human and animal studies also implicate the N1 potential in central 5-HT modulation. This is underlined by findings showing dipole sources of the auditory N1 in the primary auditory cortex which holds the highest concentration of cortical 5-HT (e.g. [28]). The N1, a negative deflection around 100 ms poststimulus with a maximum amplitude at the vertex, is modulated with the amount of allocated attention. Indeed, in the auditory domain [39],

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and similarly in the visual domain [59], it has been shown that the N1 is enhanced to target stimuli (N1 attention effect). Additional N1 sources have been identified in orbital and dorsolateral prefrontal and anterior cingulate areas and it was demonstrated that the strength of these sources was higher for target than for standard auditory stimuli (e.g. [4]). Similarly, in a series of studies using auditory choice reaction tasks, Mulert et al. [34–36] showed a close relationship between target N1 modulation and neural activity in the auditory cortex and in the ACC. Interestingly, better performance was reliably associated with enhanced N1 amplitudes and increased dorsal ACC/medial frontal gyrus BOLD activations in the N1 timeframe only for those subjects who reported to have spent much cognitive effort during the task compared to those who rated themselves low on an effort scale. In accordance with Sarter et al. [52] who coined the term attentional effort, Mulert et al. [36] defined cognitive effort as an integration of explicit and implicit motivational forces with attentional performance to optimize goal-directed behavioural and cognitive processes.

As shown, there is a strong link between target-related N1 modulation, effort and top-down attention on the one hand. On the other hand, as outlined above, the auditory N1 may reflect central 5-HT activity, and may therefore provide a good measure for possible 5-HT effects on voluntary attention: Although there is growing evidence that 5-HT is implicated in memory and learning, its role in voluntary or executive attention is not well understood. One way to examine the potential impact of 5-HT on voluntary attention is provided by genetic variation of 5-HT functioning which only recently has been extended to the cognitive domain. In this regard, a promising candidate of the human 5-HT pathway is the SLC6A4 gene encoding the 5-HT transporter (5-HTT), located at the presynaptic membranes where it performs re-uptake of 5-HT from the synaptic cleft to the nerve terminal. The 5-HTT gene contains a repeat length polymorphism in the promoter region (5-HTTLPR) which is composed of a short and a long allelic version. In vitro studies showed that the short "s" allele results in lower transcriptional efficiency than the long "l" allele and, hence, in lower serotonin transporter function [31]. However, in vivo studies using positron emission tomography and specific radiotracers showed mixed results concerning the relationship of 5-HTTLPR to serotonin transporter binding potential between genotypes (e.g. [44]). More recently, 5-HTTLPR has been found to show *developmental* effects that are associated with structural and functional changes of brain circuits [5,44]. If replicated, these developmental effects of 5-HTTLPR on mechanisms such as neurogenesis (which may not be directly linked to serotonin transporter binding) could be a plausible explanation of the numerous 5-HTTLPR-associated findings: A considerable body of evidence has implicated the s-allele in higher scores in negative emotionality [31,54] and in stronger amygdala activation in response to fearful faces [46], although inconsistent findings have been also reported (e.g. [37]). However, more diverse 5-HTTLPR-related functional and structural differences observed by Canli et al. [14] suggest a broader role of 5-HTTLPR in brain functioning, including cognitive and motor processes indicating pleiotropic effects on affective and cognitive functioning (see also Ref. [13]).

Event-related potential studies from Fallgatter and co-workers demonstrated enhanced responsiveness of prefrontal cortical areas in 5-HTTLPR s-allele carriers. Subjects with the s-allele showed stronger anteriorization of the so-called NoGo-P3, an ERP proposed to reflect mechanisms of inhibitory response control in the ACC [19], and larger amplitudes of the error-related negativity, which reflects ACC-mediated processes of conflict monitoring [20]. Furthermore, in a study of Roiser et al. [50], s-allele carriers outperformed l-allele carriers in episodic memory accuracy and showed better attentional performance during a Go/no-go task. Recently, we also presented results suggesting enhanced executive attention in s-allele carriers using a continuous performance task (CPT), and showed a second genetic variation of 5-HT functioning (TPH2), which has originally also been related to negative emotionality, to be associated with better cognitive control [47,55].

Given that the N1 is sensitive to top-down-attention, and is suggested to be predictive of 5-HT activity, the aim of the present study was to investigate whether 5-HT alterations contribute to differences in voluntary attention reflected in target N1 modulation. Based on recent evidence, we particularly expected s-allele carriers of the 5-HTTLPR to show enhanced attention allocation to target events, although an association with unattended novel events (i.e. bottom-up-driven attention) should also be taken into account [23]. To address this question, we used an auditory novelty oddball task comprising rare targets and novel sounds embedded in frequently occurring standard stimuli. For the reason that Mulert et al. [35,36] reported that individual differences in cognitive effort exert a strong influence on the target N1 we also included a reliable measure of stable individual differences in cognitive effort, the Need for Cognition Scale (for review see Ref. [12]). Because associations between negative emotionality and 5-HTTLPR have been revealed (see above), we additionally included the Neuroticism Scale of the Revised NEO-Personality Inventory [16].

2. Methods

2.1. Participants

Participants were 72 right-handed students (26 men, age M ± SD 22.3 ± 2.8 years, range 18–30 years) who gave written informed consent and received either monetary compensation or course credit for their participation. The sample has been examined previously within another context [18]. All participants confirmed to be free of relevant health problems, that they never had received psychopharmacological treatment, and did not abuse drugs. Normal hearing was ensured via audiometer. Potentially confounding factors, such as participants' sleep duration as well as their nicotine, caffeine, and alcohol consumption during the past 24 h were assessed via self-report. Cognitive effort was assessed using the short version of the German Need for Cognition scale (NFC; [6]). The German version of the Revised NEO-Personality Inventory [42] was used to measure Neuroticism (NEO-N). Four participants were excluded from the sample due to missing questionnaire or genotype data. The study was conducted in accordance with the Declaration of Helsinki and followed the standards of the German Psychological Association.

2.2. Task and procedure

Participants were seated in a dimly lit, acoustically shielded room and the electrode cap was attached. The recording session started with an 8-min resting EEG, which was part of a different project but provided the opportunity to familiarize subjects with EEG procedure. The resting EEG was followed by the auditory novelty oddball paradigm. Auditory stimuli were presented binaurally at about 70 dB by means of foam-protected air-tube insert earphones. Two sine tones of 350 Hz and 650 Hz served as frequent standard stimuli and as rare target tones, respectively. Probability of rare tones was 10% and occurrence of frequent tones was set at 80%. A third category of events (10% probability) comprised novel stimuli that were taken from a set of environmental sounds [23] and that were presented only once in pseudo-randomized order. The stimuli ($N = 500$) had a mean duration of 320 ms and were presented with a variable interstimulus interval ranging from 950 ms to 1250 ms. A short break was implemented after 250 stimuli. Participants were requested to silently count the rare target tones.

2.3. EEG recordings

EEG, vertical electrooculogram (VEOG), and horizontal electrooculogram (HEOG) were continuously recorded with a sampling rate of 512 Hz from 32 Ag/AgCl electrodes, attached to an electrode cap, and positioned according to the enhanced 10–20 system with the nose-tip as reference and AFz as ground. Electrode impedances were kept below 10 kΩ and the data were filtered using a bandpass of 0.1–100 Hz. Continuous EEGs were epoched from −200 ms to 800 ms after stimulus onset. To remove artifactual information, epochs were submitted to an infomax independent component analysis (ICA) using EEGLAB [17]. ICA-corrected epochs with values that exceeded a threshold of ±100 mV were rejected, which resulted in a median percentage of rejected trials of about 4%. The first and the second half of the epochs of each condition were averaged separately (blocks 1 and 2). To linearly decompose the ERP voltage signal, the averages were submitted to an unrestricted, unscaled temporal principal components analysis (PCA) based on the covariance matrix and followed by varimax rotation. Decomposed ERP measures provide a higher reliability and a lower degree of overlap than peak-based amplitudes and, therefore, proved to be better suited for the analysis of spatially and temporally

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