Behavioural Brain Research 284 (2015) 11–18

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Individual response speed is modulated by variants of the gene encoding the alpha 4 sub-unit of the nicotinic acetylcholine receptor (*CHRNA4*)

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HIGHLIGHTS

- We studied the effect of the CHRNA4 rs1044396 polymorphism (C/T) on response speed and selective attention in three behavioral tasks.
- The effects on response speed were uniformly consistent: Reaction times increased in dependence of the C allele dosage.
- No effects of this polymorphism on selective attention were noted.
- We show that the nicotinic acetylcholine receptor influences the speed of information processing.

ARTICLE INFO

Article history:
Received 23 October 2014
Received in revised form 16 January 2015
Accepted 22 January 2015
Available online 30 January 2015

Keywords:
Acetylcholine
Nicotinic acetylcholine receptor
CHRNA4 rs1044396
Response speed
Selective visual attention
Information processing

ABSTRACT

Acetylcholine (ACh) is a known modulator of several domains of cognition, among them attention, memory and learning. The neurotransmitter also influences the speed of information processing, particularly the detection of targets and the selection of suitable responses. We examined the effect of the rs1044396 (C/T) polymorphism of the gene encoding the nicotinic acetylcholine receptor α4-subunit (*CHRNA4*) on response speed and selective visual attention. To this end, we administered a Stroop task, a Negative priming task and an exogenous Posner-Cuing task to healthy participants ($n = 157$). We found that the *CHRNA4* rs1044396 polymorphism modulated the average reaction times (RTs) across all three tasks. Dependent on the C allele dosage, the RTs linearly increased. Homozygous T allele carriers were always fastest, while homozygous C allele carriers were always slowest. We did not observe effects of this polymorphism on selective attention. In sum, we conclude that naturally occurring variations within the cholinergic system influence an important factor of information processing. This effect might possibly be produced by the neuromodulator system rather than the deterministic system of cortical ACh.

1. Introduction

Cognitive performance is modulated in a domain-specific fashion by the cortical and subcortical availability of neurotransmitters. Acetylcholine (ACh) serves as a neurotransmitter for 10–15% of all neurons and is majorly distributed in the central and in the peripheral nervous system [1]. This neurotransmitter has been found to modulate different aspects of cognition, among them attention [2], memory and learning [3], and consciousness [4]. In this study, we will focus on the effect of ACh on response speed and selective visual attention. We will use the term "response speed" interchangeably with the term "reaction time" (RT). RT is the time interval between the appearance of a sensory stimulus and the subsequent behavioral response to it. First termed as such in 1873, differences in RT have been examined since the beginnings of experimental psychology [5]. Most RT tasks are comparatively simple and will be completed in less than one second by healthy participants. Nevertheless, RT differences are associated with complex constructs like intelligence [6] and are indicative of the speed of information processing. The sequence of information processing is initiated by the perception of a target and culminates in the motor response; in between these two brackets – the sensory

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http://dx.doi.org/10.1016/j.bbr.2015.01.041
0166-4328/

processing of the input on the one hand and the measurable reaction on the other hand – lay the processes that determine and prepare the suitable response. Commonly, these processes are referred to as the cognitive component of response speed.

1.1. The effects of nicotine on response speed

Although there are lesion studies analyzing the impact of the cholinergic system on RT (e.g., [7], found slower RTs in cynomolgus monkeys after lesions of the basal forebrain cholinergic system), the relevance of the cholinergic system on RTs has traditionally been analyzed on the basis of the consumption of agonists. Since nicotine molecules bind to the nicotinic ACh receptors (nAChRs), nicotine has frequently been used as an agonist of the cholinergic system [8]. The performance of two female rhesus macaques in a spatial cuing task [9] was observed dependent on the injection of a placebo or nicotine [10]. For both monkeys, the overall RTs significantly decreased after the consumption of nicotine. In the same study, the performance of nine tobacco smokers was compared to the performance of eight non-smokers. Immediately prior to testing, smokers consumed one cigarette of their usual brand. Smokers were significantly faster than non-smokers in the cuing task. Moreover, heavier smokers exhibited a larger RT reduction than lighter smokers. Similarly beneficial effects of nicotine on response speed have been reported for a variety of different tasks [11–15]. The findings from nicotine research demonstrate that the agonistic stimulation of nAChRs can impact on response speed, thus implicating that the cholinergic system contributes to an important aspect of information processing. However, it should be noted that these findings are not unanimous and also rely on factors such as the length and intensity of the pre-experimental exposure to nicotine, as well as acute withdrawal or long-term tolerance effects [15,16].

1.2. The effect of cholinergic genes on information processing

NAChRs are ion channels and consist of five subunits arranged to a symmetrical pentamer [17]. In the central nervous system (CNS), the most common subtype of nAChRs is the α4β2-receptor [18], which is made up of α4 and β2 subunits [19]. This high-affinity receptor possesses two binding sites [20] and is widely expressed in the thalamus and the cortex [18,21]. The stimulation of this subtype by a selective agonist (S 38232) led to larger and 'sharper' cholinergic transients (i.e., brief increases in ACh activity) in the prefrontal cortex of rats that performed a task of sustained attention. This stimulation of the α4β2-receptor was associated with an improved performance in the attention task (which was reflected in an increased hit rate for the detection of target stimuli)[1]. The *CHRNA4* rs1044396 is a polymorphism of the gene that codes for the α4-subunit. This C to T base substitution at codon 1545 is synonymous. While its functionality is not yet proven, the polymorphism has been linked to a large variety of neurocognitive phenotypes and is probably in linkage disequilibrium to one or several functional variants in the promoter or other regulatory regions of the *CHRNA4* gene [22]. Effects of this polymorphism on response speed have been reported. In a cued visual search task, the RT increased dependent on the C allele dosage [23]. A similar RT-advantage for T/T carriers has been observed in a working memory task [24]. The findings of several studies also suggest that the *CHRNA4* rs1044396 polymorphism exerts an influence on measures of attention, especially of the visuospatial subtype [23,25–28]. It was hypothesized that T allele carriers of the rs1044396 polymorphism are characterized by a greater ability to process stimuli in the attentional focus as compared to stimuli outside of the attentional focus [18]. In sum, the *CHRNA4* rs1044396 polymorphism is an ideal starting point to examine the effect of naturally occurring variations in the cholinergic system on both response speed and selective visual attention.

In this study, we examined the influence of the *CHRNA4* rs1044396 polymorphism on response speed and selective visual attention in three cognitive tasks, namely in a Stroop task [29,30], a Negative priming task [31], and an exogenous Posner-Cuing task [9]. All of these can be subsumed under the domain of selective attention, though they differ in the extent of the exogenous versus endogenous orienting of attention. Both the Stroop and the Negative priming task are non-spatial tasks in which endogenous attention is measured. In contrast, the Posner-Cuing task is a visuospatial target detection task in which exogenous attention is measured. All three tasks are well-known, classical tasks that have been studied for decades in attention research. They provide clear phenotypes on a behavioral level and are well suited to measure both response speed and selective attention (at various degrees). We expected that carriers of one or two T alleles of the *CHRNA4 rs1044396* polymorphism to display higher response speeds in each task. Referring to Greenwood et al. [18], we also expected T allele carriers to display a better performance in the task that measures visuospatial selective attention, the Posner-Cuing task. At the same time, we expected no modulatory influence of the *CHRNA4* rs1044396 polymorphism on the performance in the Stroop and Negative priming task. This assumption is based on hypothesis of Noudoost and Moore [32], according to whom the cholinergic system is more relevant for the exogenous orienting that is tested in the Posner-Cuing task.

2. Methods

2.1. Participants

The sample consisted of 157 participants from the University of Trier[2]. They were given the opportunity to get excluded from the study at any time if desired. Their median age was 21 years; 86% of the participants were female. Several control variables were assessed to evaluate the physical condition of the participants (among those variables: the consumption of nicotine, the level of physical activity and fitness, the handedness, the chronotype, and preexisting conditions of dyschromatopsia or the Attention deficit hyperactivity disorder). It took about two hours to participate in the study. During this time, the participants were not allowed to eat but could drink as much water as they liked. Ethnic data was not collected, as population stratification was unlikely in our sample[3]. At the beginning of the experimental session, the participants were informed about the purpose of the study (without any reference to the specific hypotheses). They were encouraged to show their best performance in the experiments. As an incentive, they were informed that the best four participants (with regard to response speed and precision) would receive a gift certificate worth 50 €. Regardless of their performance, all participants received course credit for their participation in the study. All had normal or corrected-to-normal vision. The experimental protocol

[1] It was also reported that the effect of nicotine on ACh transients appeared to be partly mediated by the α7 nAChR subtype. This mediation might explain some of the unanimous, complex findings that have been obtained from nicotine research.

[2] This sample is part of a larger sample that has also been analyzed in regard to several polymorphisms (see [45,46])

[3] Recently, [47] have reported on the low extent of genetic heterogeneity in German samples. In their study, only a slight north-south gradient was detectible, though this difference was still several times smaller than those between samples drawn in Germany and samples in other Germanic populations, accounting for far less than 5 % of the total variance. The present study was conducted in Trier, which is situated in middle Germany.