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Research report

Auditory event-related potentials (P3a, P3b) and genetic variants within the dopamine and serotonin system in healthy females

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HIGHLIGHTS

- We studied the dopaminergic (DA) and serotonergic (5HT) genetics of the P3a/P3b.
- 60 healthy subjects completed an auditory oddball paradigm with EEG recordings.
- The prefrontal P3a was associated with DA and 5HT genotypes.
- The parietal P3b was unrelated to DA and 5HT genotypes.
- A prefrontal component of the P3b, sensitive to DA and 5HT, was identified.

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ABSTRACT

The late positive components of the human event-related brain potential comprise electrocortical reflections of stimulus-driven attentional capture (the anteriorly distributed P3a) and top–down control detection of relevant events (the posteriorly distributed P3b). As of yet, the neuropharmacologic and neurogenetic origin of the P3a and P3b is not fully understood.

In this study, we address the contribution of dopaminergic and serotoninergic mechanisms. Sixty healthy females completed an active auditory novelty oddball paradigm while EEG was recorded. In all subjects, genetic polymorphisms within the dopamine system (dopamine transporter [DAT1], catecholamine-O-methyltransferase val158met [COMT val158met]) and the serotonin system (serotonin transporter [5HTTLPR]) were assessed.

Across genotypes, novels (relative to standards) elicited a fronto-centrally distributed P3a, and targets (relative to standards) a parieto-centrally distributed P3b. Genotypes effects were observed for both P3a (COMT, 5HTTPLR) and P3b (DAT1, COMT, 5HTTLPR) only at prefrontal electrode location (Fz). Specifically, the frontal P3a was enhanced in COMT met/met homozygotes, but not in DAT1 9R. The target-related P3b was enhanced in COMT met/met and DAT1 9R relative to its genetic counterparts, but only at frontal electrodes. This 'anteriorized' enhancement may reflect either an additional frontal component in the target-related P3 dependent on dopamine, or a more subtle shift in the neural ensemble that generates the target-related P3. Results for 5HTTLPR short allele homozygotes mimicked those in COMT met/met homozygotes.

In all, the present findings suggest involvement of frontal-cortical dopaminergic and serotoninergic mechanisms in bottom-up attentional capture (COMT val158met, 5HTTLPR), with an additional top–down component sensitive to striatal signals (DAT1).

1. Introduction

The P300 (or P3) is one of the most investigated event related potentials (ERP) in the history of cognitive neuroscience. Two subcomponents are generally distinguished: the P3a and the P3b [1,2]. The P3a (also referred to as novelty P3) is elicited by unexpected novel stimuli with frontocentral scalp topography and thought to

Abbreviations: ERP, event-related potential; EEG, electroencephalogram; DA, dopamine; DAT, dopamine transporter; COMT, catechol-O-methyltransferase; 5HT, serotonin; 5HTT, serotonin transporter; 5HTTLPR, serotonin transporter long polymorphic region; VNTR, variable number of tandem repeats.

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reflect stimulus-driven attentional capture or reorienting [3–6], or the ensuing behavioral interrupt [7]. The P3b reflects top–down controlled processing of relevant or otherwise salient events, probably involving activation of attentional networks facilitating memory operations in temporal and parietal areas [6,8,9]. Both P3a and P3b are typically recorded in so-called oddball paradigms, where infrequent novel (P3a, 10%) and target (P3b, 10%) stimuli are embedded in a stream of identical standard stimuli with a high probability (80%).

Even though the P3 and its subcomponents have been investigated for nearly fifty years since the first report in literature [10], their neuropharmacology and neurogenetic background are still poorly understood with a plethora of neurotransmitters involved [1,7]. For the P3a, mainly dopaminergic (DA) mechanisms have been inferred [see [1,2] for a review] from studies involving Parkinson's disease [11–13], administration of dopaminergic agents [14–16] and studies on dopaminergic genes [17–21,; but see 22, 23] described in more detail in the discussion. In contrast, the P3b has been associated mostly with noradrenergic (NE or NA) neurotransmission, based on theoretical considerations [1,7,9], neuropharmacological and neuropsychological data in animals and humans regarding the role of the locus coeruleus in P3b generation [see [9] for a review], and analysis of genetic associations that were not driven by specific hypotheses on candidate NE-related genes [17,24]. As apparent from reviews [e.g., see Table 5 within [7]], it should be noted that other neurotransmitter systems such as acetylcholine and GABA have also been implicated in P3b generation.

Pharmacological challenges and patient-studies employing neurotransmitter-specific disorders are fruitful approaches for investigating involvement of neurotransmitter systems in neurophysiologic processes. Studying correlates of innate variability within the target transmitter system is another approach, allowing for the assessment of involvement of these systems in such processes. This is often achieved by means of candidate gene studies where known polymorphisms previously linked to brain neurotransmitter levels are used as indices of the activity of particular transmitter systems. Pharmacological approaches suffer from potentially excessive demands on participants, especially in relation to establishing (individual) dose response curves, and the availability of patients for research. Furthermore, there is often a paucity of pharmacological agents, in particular for those with plausible specificity with respect to the affected neurotransmitter system. Such objections do not hold for studies investigating innate variability within the target transmitter system, although the latter potentially confounds development factors and acute effects. Given the well-documented existence of relevant genetic polymorphisms, and the high heritability of the P300, which meta-analyses estimate to be between 60% [25] and 69% [26], the genotype approach was adopted for the present study. Specifically, we addressed associations with three a priori chosen candidate polymorphisms. Unlike previous studies, these included DA-related polymorphisms with different expression patterns in cortical versus subcortical regions, as well as the well-documented serotonin transporter polymorphism.

More specifically, we selected two candidate polymorphisms previously linked to brain DA levels, the COMT val158met and the DAT1 VNTR. COMT is a dopamine-degrading enzyme (amongst other catecholamines) that serves as the main mechanism of DA clearance in the prefrontal cortex, whereas striatal DA degradation is hardly affected by COMT [27–29]. The COMT gene comprises a common single nucleotide polymorphism (SNP) at codon 158, where a nucleotide substitution from G to A results in an amino acid change from valine (val) to methionine (met). This exchange is associated with a three-to-four fold reduction of enzymatic activity due to the decrease in thermostability of the enzyme. Ultimately, the val-to-met exchange leads to higher tonic brain DA levels [30–32], making it a suitable candidate polymorphism for neurogenetic studies of DA transmission.

As a second DA candidate, we chose to investigate the DAT1 VNTR, referring to a variable number of tandem repeats (VNTR) polymorphism within the dopamine transporter (DAT) gene. In contrast to the COMT, the DAT is highly abundant in the striatum, where it serves as the key protein for DA reuptake [33,34]. The gene coding for the DAT (DAT1) contains a VNTR polymorphism that determines transporter availability [35–37] and hence, striatal DA reuptake. This ultimately results in changes of striatal DA levels, which makes the DAT1 VNTR a suitable polymorphism for neurogenetic studies of DA transmission. Combining the differential distribution of COMT and DAT in the human cortex versus subcortex allows for a comparative investigation of the role of prefrontal DA (COMT val158met) versus striatal DA (DAT1 VNTR) in P3a and P3b generation. Based on current frameworks [1,2] with regard to the neuropharmacology of the P3a and P3b and the prior studies described above, we expected the genetic variants linked to high tonic brain DA activity (DAT1 9R, COMT met/met) to be linked to heightened P3a amplitude and not so much the P3b.

In addition to dopaminergic and noradrenergic contributions to the P3a and P3b, serotonin has been suggested as a possible modulator of these neurophysiological potentials either through direct effects [1,38] or by interacting with other relevant neurotransmitters such as DA or NE [7,39]. Within the serotonin transporter long polymorphic region (5HTTLPR), the presence or homozygosis of the short allele is associated with low serotonin transporter expression and therefore low turnover of 5-HT [40]. Behaviorally, the short allele has been associated with neuroticism and harm avoidance [41,42]. These effects are accompanied by reports of 5HTTLPR dependent brain activity mostly attributed to the amygdala [43], the insula [44,45], and, by means of prefrontal-amygdala coupling, the prefrontal cortex [46–48]. These structures also play a pivotal role in orienting attention, a process that the P3a is supposed to reflect [for an overview, see 49, 50]. Therefore, 5HTTLPR short allele carriers are hypothesized to react stronger to unexpected and potentially threatening novel stimuli, which would translate to increased P3a amplitudes within an oddball paradigm.

However, literature on serotonergic modulations of the P3 is conflicting. More specifically, acute tryptophan depletion, a dietary challenge in humans that decreases 5HT synthesis acutely, failed to modulate P3 amplitudes in a two-stimulus oddball paradigm [51]. Another technique to alter brain 5HT levels, administration of serotonergic agents, produced rather inconsistent results with regard to the P3. Neither administration of the serotonergic antagonist methysergide [52] nor challenging healthy subjects with the 5HT1a agonist buspirone [53] affected P3 amplitudes. Likewise, challenging healthy subjects with escitalopram, a selective serotonin reuptake inhibitor (SSRI) failed to affect P3 amplitude [54,55]. However, administrations of clomipramine (a combined norepinephrine and serotonin reuptake inhibitor) and fluoxetine (an SSRI) have shown to decrease P3 amplitude [56].

Given this rationale, sixty healthy females were genotyped for the latter dopaminergic and serotonergic polymorphisms and subjected to a well-established auditory novelty oddball paradigm while EEG was recorded.

2. Methods

2.1. Subjects

As part of a larger study [57], sixty healthy female subjects (mean age = 20.87, SD = 1.98) were recruited via advertisements at Utrecht University, the Netherlands.