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The role of DAT1 gene on the rapid detection of task novelty

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ABSTRACT

In an environment with a myriad of different stimuli, the fast detection of novel and behaviorally relevant signals becomes crucial for an adaptive behavior. The detection of task-novelty has been related to striatum-prefrontal cortex (PFC) pathways involving dopaminergic (DA) neurotransmission. Here we thus tested the hypothesis that DA regulates the detection of task novelty through the modulation of the auditory N1 potential, an auditory potential peaking at 100 ms and previously shown to be modulated by the detection of sensory novelty. Thirty-five healthy volunteers were divided in two groups according to the presence or absence of the 9-repetition allele (9R) of the SLC6A3/DAT1 gene for the dopamine transporter. Participants performed a cued task-switching paradigm that dissociated the effects of exogenous sensory novelty from those of endogenous task novelty. Individuals with the 9R allele showed an amplitude enhancement of the auditory N1 elicited to sensory changes requiring a task-set reconfiguration as compared to sensory changes with no task novelty. In contrast, individuals without the 9R allele did not have their N1 waveform modulated by task novelty. The present results suggest that individuals homozygous for the 10-repeat allele fail to detect the behavioral relevance of new stimuli at early stages.

1. Introduction

An adaptive behavior in everyday situations requires the rapid detection and flexible integration of contextual information allowing for fine-grained adjustments to environmental demands. This rapid detection of task-relevant sensory changes has been proposed to depend on a fast route for processing environmental changes which could have immediate behavioral consequences (Barcelo & Knight, 2007; Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005; Johnston & Everling, 2006). Such route is thought to involve phasic dopaminergic (DA) responses regulated by well-defined closed-loops between the striatum and the PFC (McHaffie, Stanford, Stein, Coizet, & Redgrave, 2005; Seamans, Gorelova, Durstewitz, & Yang, 2001). From this theoretical perspective, such DA responses might modulate the early detection of task novelty in a sensory change (Redgrave & Gurney, 2006). The dopamine transporter (DAT) is the most important regulator of DA at human striatum (Garris & Wightman, 1994; Hurd, Suzuki, & Sedvall, 2001). DAT mediates the active reuptake of DA from the synapse and critically regulates the extent to which DA diffuses in the extracellular space, and thus, the duration of cellular action of DA, especially in the striatum (Sesack, Hawrylak, Matus, Guido, & Levey, 1998).

In humans, the earliest electrophysiological brain response reflecting auditory processing at cortical level, known as the N1 auditory evoked potential, has been previously proposed as a marker of bottom-up sensory processes, such as attentional capture for subsequent access to consciousness (Jaaskelainen et al., 2004; Naatanen & Winkler, 1999). However, the auditory N1 waveform does not represent a unitary stimulus-evoked process, but rather a compound of several simultaneous activations from different neural generators (Naatanen & Winkler, 1999). At least three exogenous (i.e., depending upon the physical characteristics of sensory stimulation) and three endogenous (i.e., depending upon subject's state or the informative value of the stimuli) components seem to be concurrently activated to generate the auditory N1 waveform (Naatanen & Picton, 1987). Some of these components are known to be sensitive to attentional modulations (Woldorff et al., 1993). A non-specific component of the N1 waveform was proposed to be related to the occurrence of potentially relevant events that prime the production of appropriate motor responses (Naatanen & Picton, 1987). More recently cued task-switching studies have observed an early negative frontocentral response peaking around 100 ms post-cue onset which was modulated by the task relevance of the cue (Barcelo, Escera, Corral, & Perianez, 2006; Brass et al., 2005). A

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similar modulation by the task relevance of the cue has also been reported in the visual modality (Wylie, Javitt, & Foxe, 2003).

The present study tested the hypothesis that the DA display regulates the rapid detection of task novelty (i.e., any change in stimulus–response mappings that is relevant for accomplishing the current behavioral goal). This rapid detection of task novelty is expected to influence at least some early generators of the auditory N1 evoked potential, i.e., circa 100 ms. For this purpose, a sample of healthy volunteers was divided into two groups according to a functional variable number of tandem repeat (VNTR) polymorphism identified in the 3′-untranslated region of the SLC6A3/DAT1 gene with repeat copy number ranging from 3 to 11, being 9- and 10-repeat (9R and 10R) the most frequent in the human population (Vandenbergh et al., 1992). The 10R allele has been associated with larger gene expression in vitro (Fuke et al., 2001; Mill, Asherson, Browes, D'Souza, & Craig, 2002; VanNess, Owens, & Kilts, 2005) although in vivo results are controversial: while some support the effect found in vitro (Heinz et al., 2000), other have reported lower DAT binding associated to the 10R allele (Jacobsen et al., 2000; van Dyck et al., 2005). On the other hand, a linkage study associated the SLC6A3/DAT1 gene region with heritage of the attention deficit and hyperactivity disorder (ADHD; Friedel et al., 2007), a disorder characterized by inattentional symptoms related to abnormalities in the frontostriatal network (Bush, Valera, & Seidman, 2005). Specifically, the 10R allele has been associated with the presence of such disorder (Hawi et al., 2010; Yang et al., 2007). Moreover, reduced striatal activity has been found for children with ADHD and their unaffected siblings who were homozygous for the 10R allele (Durston et al., 2008).

We hypothesized that the slower attentional orienting found in 10R homozygous (Bellgrove et al., 2007) would be due to a lack of rapid detection of behavioral relevance of the stimuli. In order to test this hypothesis, we measured the fronto-central N1 potential, which has been long related to the detection of sensory novelty (Naatanen & Winkler, 1999), and only very recently also to the early evaluation of task novelty in a task-switching paradigm (Barcelo et al., 2006; Barcelo, Perianez, & Nyhus, 2007). In so doing we employed a cued task-switching paradigm where acoustic sensory changes could be either accompanied or not by a switch in task set, thus allowing us to dissociate the effects of sensory novelty from those of task novelty.

2. Materials and methods

2.1. Participants

Forty individuals (eight men, mean age 22 ± 4.2 years, range 18–29 years) participated in the study. They were recruited from a larger sample of volunteers which were interviewed according to an adapted version of the Clinical Interview of the Diagnostic and Statistical Manual (DSM IV-R), for exclusion of subjects with neurological and psychiatric illness, phobias, and drug consumption. All participants gave informed consent at each phase of the study (interview, buccal cells extraction and EEG recordings) according to the Declaration of Helsinki and the Ethic Committee of the University of Barcelona. All subjects had normal or corrected-to-normal vision and normal audition. After exclusion by diagnostic criteria and after obtaining the SLC6A3/DAT1 polymorphisms, the participants showing the most frequent genotypes (9R/9R, 9R/10R, 10R/10R; Vandenbergh et al., 1992) were selected for an EEG recording session. Participants genotyped as 10R/10R were assigned to the 9R− group and those genotyped as 9R/10R and 9R/9R were included in the 9R+ group. Five participants were excluded from the analyses due to a large amount of artifacts in their EEG recordings. From the remaining 35 individuals, eighteen composed the 9R+ group and seventeen subjects were included in the 9R− group. Participants from each of the two genetic groups did not differ significantly in age, gender and state or trait anxiety scores (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

2.2. DNA isolation and genotyping

In order to genotype the participants for the SLC6A3/DAT1 gene, DNA was first collected with cheek cell swabs and extracted using the Epicentres® BuccalAmp™ DNA Extraction Kit (Epicentre, Madison, WS). Upon isolation of DNA, the 40-bp VNTR polymorphisms for the DAT1 gene (rs#28363170) were obtained for each DNA sample following similar procedures as those described by Sano, Kondoh, Kakimoto, and Kondo (1993), modified by amplifying PCR-VNTR using a fluorescently tagged primer. Amplification products were analyzed using a capillary electrophoresis on the sequencer ABI Prism® 3730 (Applied Biosystems, Foster City, CA) and through the Fragments Analysis Technique with GeneMapper® Software Version 4.0 (Applied Biosystems, Foster City, CA).

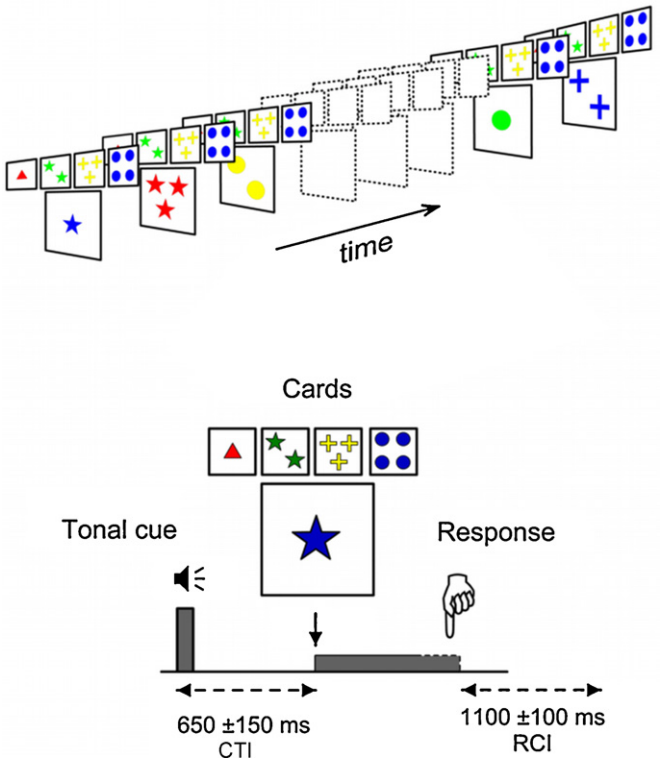

Fig. 1. Stimulus material and experimental design. Each trial consisted of a tonal cue followed by a visual target display with four key cards on top of one choice card. Subjects were instructed to classify targets according to their color or to their shape. Before target onset, a tonal cue (500/1000 and 2000/4000 Hz tones) informed whether to classify according to the color or the shape rules. The meaning of the two tones was counterbalanced across subjects. The length of the cue-target interval (CTI) and the response-cue interval were jittered.

2.3. Behavioral procedure

A task-cueing protocol inspired by the Wisconsin Card Sorting Test (WCST; Rubinstein, Meyer, & Evans, 2001) and adapted for measuring event-related brain potentials (ERPs; Barcelo, 2003) was administered to participants. Each trial consisted of a tonal cue followed by a target display with four key cards on top of one choice card, all centered on a computer screen. The target stimulus subtended a visual angle of 4° horizontally and 3.5° vertically, and remained on display until a response was given or up to a maximum of 3000 ms. Subjects were instructed to match the choice card with one of the four key cards following two possible task rules (color or shape). To ensure that all participants could see colors properly, the Test of Ishihara was applied for excluding participants with suspected color blindness. Before target onset, one out of four tonal cues explicitly informed the subject whether to sort the card according to either the 'color' (500/1000 Hz) or 'shape' (2000/4000 Hz) rules (Fig. 1). The meaning of the tonal cues was reversed for half of the subjects. Three trial types were defined in order to dissociate the processing of changes in sensory and task representations. In *repeat* trials, both the tonal cue and the task were repeated relative to the previous trial. In *cue-switch* trials, only the cue changed but the task remained the same as in the previous trial. In *task-switch* trials both cue and task changed. Therefore, this design allowed for an independent manipulation of cue-switches involving only a change in sensory stimulation, and task-switches, involving a change in both sensory tonal cue and higher-order task rules. Hence, the comparison of cue-switch and task-switch trials permitted to independently probe the updating of sensory and task-rule representations in working memory (Barcelo, Perianez, & Knight, 2002; Barcelo et al., 2006). Responses were made using 4 keys on a keyboard, mapped onto the four fingers of the dominant hand, in an array corresponding to the layout of the four key-cards. The far left button designated the key card on the far left of the display; the far right button designated the key card on the far right, and so on. Binaural tones were delivered through Sehnheiser® HD202 headphones with a duration of 200 ms,

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10 ms rise/fall times and 65 dB SPL. All stimuli were presented with the stimulation program Presentation® (Neurobehavioral Systems Inc., Albany, CA). All three trial types were randomly presented with the same overall probability along the 200 trials of the experimental block, as well as during the 50 practice trials. The cues related to each criterion were employed five times during the instruction period of the practice block, and three more times during the instructions of the experimental block, in order to ensure that each participant had correctly learnt the cue-task association. Whenever the hit rate of the practice block was lower than 75%, an additional practice block was administered to ensure full assimilation of the correct cue-task association prior to the experimental run. All task sets declared in the instructions consisted of four-feature-stimulus to four-forced-response mappings. 'Task set' denotes here, in a broad sense, a set of rules that govern the mapping between sensory inputs and motor responses (Braver, Reynolds, & Donaldson, 2003). The cue-target interval randomly varied between 650 ± 150 ms, thus minimizing the effects of a constant preparation interval (Rogers & Monsell, 1995), and the target remained on the screen until a response was given (and up to a maximal of 3000 ms). Response-cue intervals also varied randomly around 1100 ± 100 ms within the trial block.

2.4. EEG data acquisition

EEG activity was recorded (ANT® Software b.v., Enschede, The Netherlands) during task performance from 64 scalp electrodes following the extended 10/10 convention in an electrically and acoustically shielded room. Horizontal and vertical electro-oculographic (EOG) recordings were obtained with electrodes placed at the outer cantus of the right eye and above the right eye. The common reference electrode was placed on the tip of the nose, and the ground was located at the chest. The EEG was amplified and digitized at a sampling rate of 512 Hz. Impedances were kept below 10 kΩ during the whole recording session, which lasted about 20 min.

2.5. Data processing

Cue-locked ERPs were averaged offline for each trial type (repeat, cue-switch and task-switch), for an epoch of 800 ms including a pre-stimulus baseline of 200 ms. The first five trials of the block were excluded from analysis. Frequencies above 30 Hz were digitally filtered out from individual EEG epochs prior to ERP averaging. EOG correction was performed via a blind source separation technique with ASA 4.5 of ANT® Software (Enschede, The Netherlands), as described in Belouchrani, Abed-Meraim, Cardoso, and Moulines (1997). After EOG correction, any epochs containing EEG activity exceeding ±100 μV peak-to-peak amplitudes were rejected from further analysis. The mean percentages of clean EEG epochs retained for ERP averages were 74.4%, 75.1% and 72.7% epochs from the repeat, cue-switch and task-switch conditions, respectively, and these did not differ among the three task conditions.

2.6. Data analysis

For behavioral analysis, any correct button press within 200–3000 ms after target onset was regarded as a hit, and the mean RT was computed for hit trials only. Hit rate and mean RT were submitted to a two-way mixed ANOVA with one repeated-measures factor (Trial type: repeat, cue-switch, task-switch), and one between-subject factor (Group: 9R+ and 9R−). Pair-wise post hoc comparisons were performed to examine significant difference between conditions.

For the analysis of the auditory fronto-central N1 component, the mean amplitudes were computed in the latency window from 110 to 140 ms and the latencies of local minimums from 70 to 150 ms. Both variables were computed at channels F3, F4, Fz, C3, C4, Cz, P3, P4 and Pz. Three-factor repeated-measures ANOVAs were performed including three within-subjects factors: Trial type (repeat, cue-switch and task-switch), Fronto-perietal levels (three levels for frontal, central and parietal channels) and Laterality (three levels for the left, middle and right channels), as well as the between-subject factor Group (9R+ and 9R−). Pair-wise post hoc comparisons were performed between all trial types to examine whether any trial type effect was due to a switch in cue or in task. The Greenhouse-Geisser correction was applied to the degrees of freedom of the ANOVAs, and the corrected p-values were reported whenever appropriate. In order to parcel the location of the effect, an ANOVA was performed with Trial type (task-switch compared to cue-switch) and Laterality across all three levels of frontality for 9R+ individuals.

3. Results

Individuals from both groups showed reduced accuracy following any tonal change (main effect of Trial type: $F_{2,66} = 39.8$, $p < 0.001$) which was due to lower hit rates in task-switch compared to cue-switch trials ($F_{1,33} = 54.0$, $p < 0.001$; Fig. 2a). No effect of Group was found for the hit rate. Longer mean RTs after a tonal switch (main Trial type effect: $F_{2,66} = 100.7$, $p < 0.001$) were also observed, due to slower responses in cue-switch compared to repeat trials ($F_{1,33} = 123.6$, $p < 0.001$), as well as in task-switch compared to cue-switch trials ($F_{1,33} = 9.0$, $p = 0.005$). Although the two DAT1 groups did not differ significantly in their mean RT, the most relevant behavioral result was a significant Trial type × Group interaction due to the slower response in cue-switch compared to repeat trials for the 9R+ but not the 9R− group ($F_{1,33} = 6.6$, $p = 0.015$). Likewise, while 9R− individuals showed a further increase in mean RTs between cue-switch and task-switch trials ($F_{1,16} = 16.5$, $p = 0.001$) this increase was not observed for the 9R+ group (Fig. 2b).

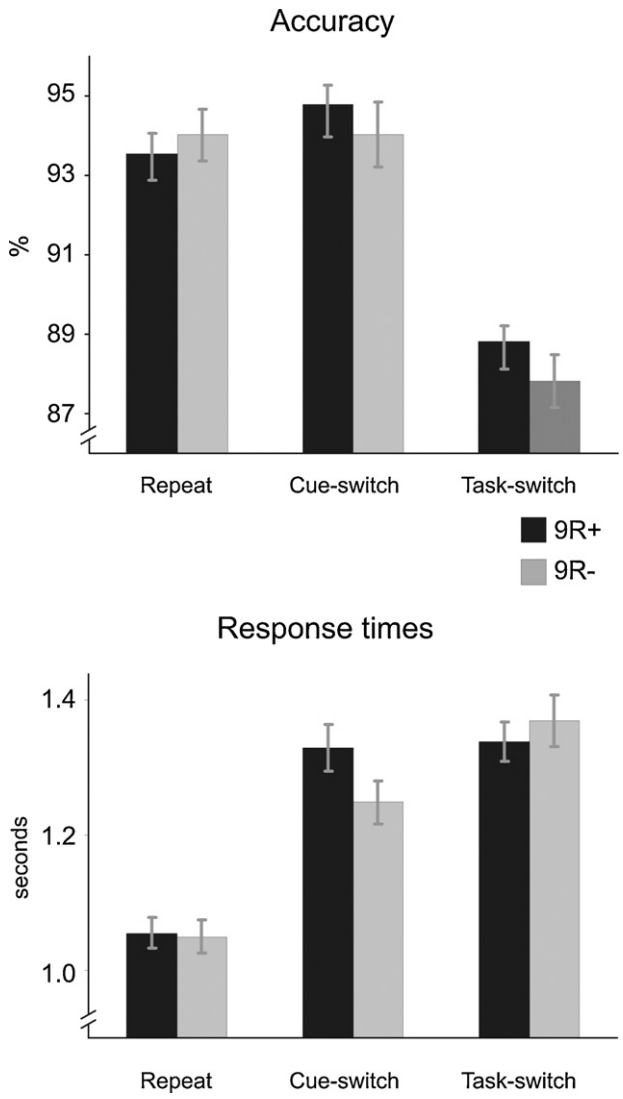

Fig. 2. Accuracy and response times (RT) for the 9R+ and 9R− groups across the three trial types. The accuracy was lower in task-switch trials as compared to the other two trial types, with no differences between the groups. The RT plot shows a delay in cue-switch trials for both groups; however, whereas the 9R− group showed larger RT in task-switch as compared to cue-switch trials, the 9R+ group showed similar RT for these two trial types.

The frontocentrally distributed N1 waveform peaked at 111, 111 and 116 ms for 9R+ individuals and at 107, 113 and 112 ms for 9R− individuals in repeat, cue-switch and task-switch trials, respectively. The overall 3 × 2 ANOVA design revealed a significant Trial Type × Group interaction for N1 amplitudes ($F_{1,33} = 5.12$, $p = 0.030$; Fig. 3a). Post hoc test of effects revealed larger N1 amplitudes in task-switch relative to both cue-switch and repeat trials for the 9R+ group (with $F_{1,17} = 7.50$, $p = 0.014$ for the post hoc comparison task-switch vs cue-switch trials on the 9R+ group), with no similar effects for the 9R− group. This interaction was significant at frontal ($F_{1,17} = 14.2$, $p = 0.002$) and central channels ($F_{1,17} = 7.9$, $p = 0.012$), but not over more posterior scalp locations

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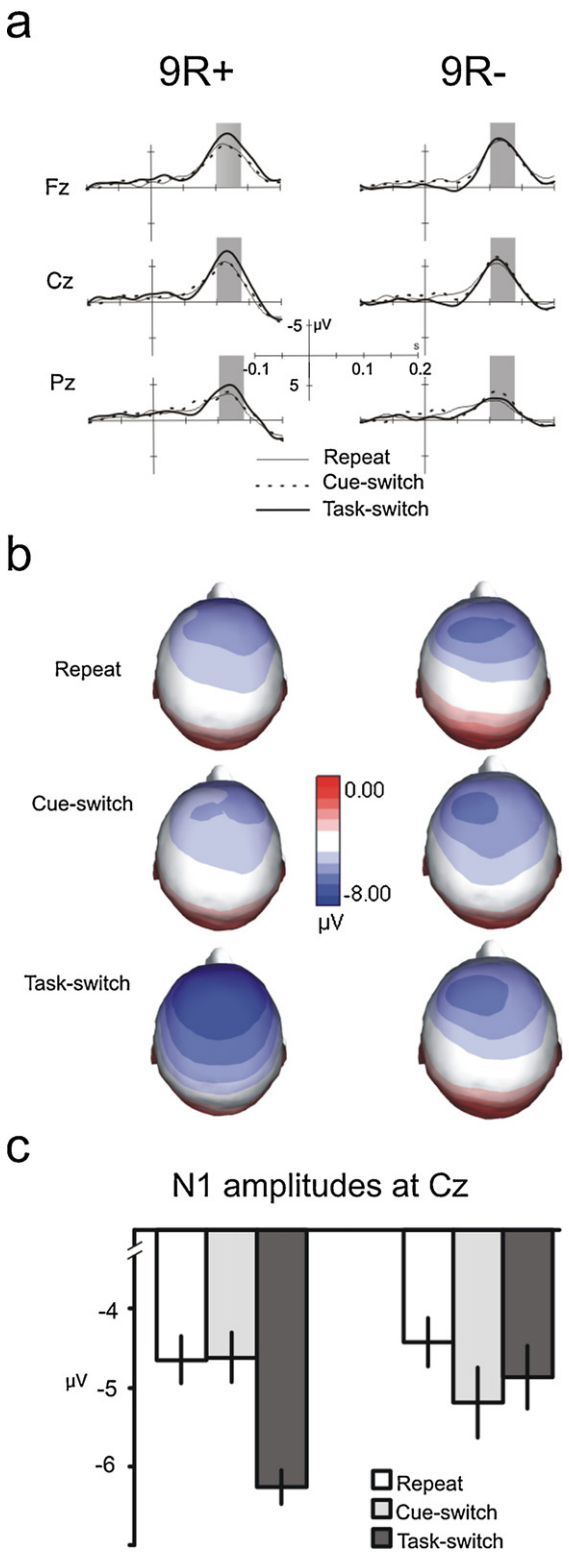

Fig. 3. The N1 auditory evoked potential. (a) Cue-locked brain waves at Fz, Cz and Pz locations for 9R+ and 9R− individuals across the three trial types. Notice that 9R+ individuals display an amplitude enhancement for task-switch as compared to cue-switch trials, which is not observed in 9R− individuals. (b) Scalp distribution of the brain response in the three trial types for both 9R+ and 9R− individuals. The effect of task-switching compared to cue-switching in the shadowed time windows displayed by 9R+ shows a frontocentral distribution. In contrast, 9R− individuals show no specific effect for task-switch in such subcomponent. (c) Amplitudes of the frontocentral N1 component at the Cz electrode in the three trial types and for the two groups. Larger amplitudes in task-switch trials relative to cue-switch and repeat trials were observed in the 9R+ but not in the 9R− group.

(Fig. 3b). For 9R+ individuals, the mean amplitudes of the frontocentral N1 waveform at Cz were −4.6, −4.6 and −6.2 μV for repeat, cue-switch and task-switch trials, respectively. For 9R− individuals mean N1 amplitudes at Cz were −4.4, −5.2 and -4.8 μV in repeat, cue-switch and task-switch trials (Fig. 3c). No main effects or interactions were observed for peak latencies.

4. Discussion

The present study aimed at examining whether DA regulates the rapid detection of behaviorally relevant sensory changes by means of the SLC6A3/DAT1 genetic polymorphism. The current results revealed that 9R+ individuals showed an enhancement of the frontocentral N1 waveform peaking as early as 110 ms following a cue signaling a switch compared to a cue signaling repetition in the stimulus–response mappings of the ongoing task-set. In contrast, the amplitude of the early frontocentral N1 waveform failed to show any enhancement associated to the behavioral relevance of the cue for 9R− individuals in spite of their significantly increased mean RTs in cue-switch as compared to repeat trials, as well as in task-switch as compared to cue-switch trials.

We predicted that the rapid detection of task novelty would involve at least some generators of the N1 waveform, the earliest brain response reflecting auditory processing at cortical level (Naatanen & Winkler, 1999). Accordingly, the 9R+ group displayed an enhancement of the N1 waveform for behaviorally relevant cues. Several exogenous and endogenous components are known to be involved in the generation of this N1 waveform (Naatanen & Picton, 1987), some of which are sensitive to attentional manipulations (Woldorff et al., 1993). The scalp distribution of the amplitude enhancement found in the current study argues for a frontocentral N1 sub-component that is sensitive to both stimulus significance (Naatanen & Picton, 1987) and task novelty (Barcelo et al., 2006; Brass et al., 2005). However, 9R+ individuals showed similar mean RTs to cue- and task-switch trials, in agreement with a related study in which we found a similar stereotypy of the novelty-P3 brain response for these two trial types (Garcia-Garcia, Barcelo, Clemente, & Escera, 2010), suggesting that 9R+ individuals responded to each cue independently from the immediate context, that is, irrespective of the meaning of the previous trial for switching or repeating the task.

However, the currently reported data shed some light on the interpretation of the behavioral outcomes of these groups during task-set reconfiguration. It seems paradoxical that the observed group dissociation in the early N1 amplitude did not directly translate onto distinct behavioral task-switch costs, since 9R+ individuals showed similar behavioral costs in cue-switch and task-switch trials. Next we offer two plausible explanations for this paradoxical dissociation between N1 amplitudes and behavioral switch cost. The first hypothesis that this dissociation could be attributed to distraction (Escera, Alho, Schroger, & Winkler, 2000; Escera, Alho, Winkler, & Naatanen, 1998; Escera & Corral, 2007; Escera, Yago, Corral, Corbera, & Nunez, 2003), based on the observation that 9R+ individuals invested about 100 ms extra time than the 9R− group in cue-switch trials involving a task-irrelevant sensory change. Perhaps this advantage in neural processing indexed by enhanced N1 amplitudes could also result in slightly increased distractibility for 9R+ (i.e., longer RTs after a sensory change; Gaymard, Francois, Ploner, Condy, & Rivaud-Pechoux, 2003), as revealed by the group comparison for cue-switch relative to repeat trials. This slower responding to task-irrelevant sensory changes could be due to an excess of protection against interference (Cools, Barker, Sahakian, & Robbins, 2001). From this perspective, the putatively larger DA display in frontostriatal circuits of 9R+ individuals would not only favor early novelty detection, but would also help protect

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the current task-set in the presence of competing novel sensory or task demands (cf., Cools et al., 2001), resulting in larger times deployed to the evaluation of sensory changes. This idea would also be supported (and neurophysiologically indexed) by the larger amplitudes found in the novelty-P3 brain responses of 9R+ relative to 9R− individuals (Garcia-Garcia, Barcelo, et al., 2010; Garcia-Garcia, Clemente, Dominguez-Borras, & Escera, 2010), suggesting a more efficient context-updating process, leading to larger switch costs

Alternatively, one could assume that the N1 waveform which is enhanced for task-switch relative to cue-switch trials only in 9R+ individuals, reflect a preparatory mechanism that when potentiated leads to a reduction in the time taken to reconfigure of stimulus–response mapping, even though the actual reconfiguration takes place at later stage of processing. This proposal would be consistent with Karayanidis, Provost, Brown, Paton, and Heathcote (2010) argument about the functional role of later ERP components on the final task-switch cost. Supporting this view, it can be noticed that while 9R+ individuals show and increase in N1 amplitude, without a corresponding RT delay for task-switch compared to cue-switch trials, 9R− individuals fail to show that early increase on the putatively preparatory response, and as a consequence, they experience a delay in RT for reconfiguring the mental task set.

Importantly, only 9R+ individuals showed such an early detection of the task novelty conveyed by sensory changes. The important role of DA in attentional control such as the detection of salient stimuli (Wilson & Bowman, 2006) or task-switching (Cools, 2008; Garcia-Garcia, Barcelo, et al., 2010; Garcia-Garcia, Clemente, et al., 2010) has been widely evidenced by previous studies. It has been hypothesized that DA expression is regulated by closed-loops between the striatum and the PFC (Seamans et al., 2001), as part of a route associated with the attentional capture by environmental changes which have immediate behavioral consequences (Barcelo & Knight, 2007; Brass et al., 2005; Johnston & Everling, 2006). These prefrontostriatal loops may account for the current findings arguing for a crucial role of DA activity on the early detection of task novelty. Accordingly, recent studies evidenced a facilitation of very early novelty processing by reward-motivation (Bunzeck, Doeller, Fuentemilla, Dolan, & Duzel, 2009), possibly related to the elevated levels of striatal DA in the context of reward (Niv, Daw, Joel, & Dayan, 2007). In a similar manner, our results show that the detection of task-novelty might be regulated by striatal DA, and are in accordance with the evidence relating the 10R allele with a higher expression of DAT (Durston et al., 2008; Fuke et al., 2001; Garcia-Garcia, Barcelo, et al., 2010; Garcia-Garcia, Clemente, et al., 2010; Hawi et al., 2010; Heinz et al., 2000; Mill et al., 2002; VanNess et al., 2005). It seems plausible that cortical-subcortical connections like prefrontostriatal pathways offer a potential circuit for the rapid detection of unexpected and potentially relevant sensory signals (Gaymard et al., 2003), as enough information can be conveyed through this route to detect a mismatch between sensory input and active PFC representations (Barcelo & Knight, 2007; Johnston & Everling, 2006; Potts, Martin, Burton, & Montague, 2006; Redgrave & Gurney, 2006).

The results obtained in the present study can shed some light on our understanding of cognitive deficits in DA-related disorders such as ADHD, which has also been related to a poor ability to flexibly adjust behavior to environmental demands (Nigg & Casey, 2005). Previous studies have revealed that children with ADHD show reduced enhancement of auditory cortex activation to behaviorally relevant auditory stimuli (Jonkman et al., 1997; Loiselle, Stamm, Maitinsky, & Whipple, 1980). Moreover, similarly to 9R− participants in the current study, ADHD adults have been also reported to show a lower enhancement of the amplitude of the N1 waveform to auditory cues indicating an attentional switch (Bekker et al., 2005). Accordingly, ADHD has been linked to the 10-repeat allele (Yang et al., 2007), and is characterized by inattentional symptoms related to abnormalities in the frontostriatal network (Bush et al., 2005). The pharmacological treatment of ADHD aims to raise DA levels in the striatum by increasing the signal-to-noise ratio in target neurons (Volkow et al., 2001). Because reduced striatal activity has been found for children with ADHD and their unaffected 9R− siblings (Durston et al., 2008), deficient striatal DA activity might account for the failure in the early detection of behavioral relevance, which might help to understand the poor adjustment to environmental demands presented in ADHD patients (Nigg & Casey, 2005). Although the small size of the sample might be regarded as a limitation of the present study, all this evidence point to the N1 waveform as a useful endophenotype indicative of inattentive symptoms of ADHD, and could thus aid the design of pharmacological treatments of attention-related disorders.

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