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RESEARCH ARTICLE

Dopamine, norepinephrine, and the management of sensorimotor bindings: individual differences in updating of stimulus–response episodes are predicted by DAT1, but not DBH5′-ins/del

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Abstract Evidence suggests that the flexibility of managing (creating and updating) stimulus–response bindings is driven by the dopaminergic system. Given that striatal dopamine (DA) plays a crucial role in the updating of working memory, the present study tested whether individual differences in the efficiency of updating stimulus–response episodes (event files) are predicted by differences in genetic predisposition related to the efficiency of the striatal dopaminergic pathway. In view of contrasting claims that stimulus–response binding is related to norepinephrine, we also considered genetic predispositions regarding noradrenergic pathways. In a sample of 100 healthy adults, we studied whether the degree to which stimulus–response bindings affect ongoing performance is predicted by polymorphisms of the dopamine transporter gene (DAT1, associated with striatal DA levels) and DBH5′-ins/del (strongly correlated with dopamine beta-hydroxylase, the enzyme catalyzing the dopamine-norepinephrine conversion). The performance of 9-repeat carriers of the DAT1 gene was more affected by stimulus–response bindings than the performance of 10/10 homozygotes was, while DBH5′-ins/del polymorphism was not related to performance. This outcome pattern suggests a crucial role of the nigrostriatal dopaminergic pathway in the flexible management of stimulus–response episodes, whereas norepinephrine does not seem to play a role.

Keywords Binding problem · Event file · Dopamine · DAT1 gene · Norepinephrine

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Introduction

One of the basic characteristics of the primate cortex is that it represents the external world in a distributed fashion. For example, a visually perceived external object like a yellow ball will not be represented by a single code but by a multitude of feature-related codes in different representational maps. Our brain is able to correctly integrate the feature codes that belong to the same object, presumably by means of the temporal synchronization of those cell populations that represent the different features of a given object (Abeles 1991). Feature binding is not restricted to visual features and objects but spans entire stimulus–response episodes, the features of which are more or less automatically integrated into so-called event files (Hommel 2004).

Given the speculation that the creation and handling of feature bindings might be related to neural synchronization (for overviews, see Engel and Singer 2001; Jensen et al. 2007) and evidence from animal studies that neural synchronization is related to particular neurotransmitter systems (e.g., Rodriguez-Bermudez et al. 2004), a number of studies have started to look into the relationship between neurotransmitter systems and the creation and handling of feature bindings in humans. Even though the mechanisms underlying this relationship are not yet fully understood, an interesting double dissociation between bindings of stimulus features and bindings of stimulus and response features has been reported. On the one hand, the integration and/or retrieval of different features related to the same visual stimulus has been found to be mediated by drugs affecting muscarinic cholinergic pathways (Colzato et al. 2004, 2005), while manipulations likely to affect nicotinic cholinergic pathways (Colzato et al. 2005) or dopaminergic pathways (Colzato et al. 2007a, b) had no impact on the handling of visual features. On the other hand,

however, increasing evidence suggests that the updating of stimulus–response bindings is mediated by dopamine (DA). For instance, the updating of stimulus–response episodes has been found to be modulated by the presentation of affect-inducing pictures (Colzato et al. 2007a), which can be assumed to stimulate the dopaminergic system (Ashby et al. 1999, 2002), and by the rate of the spontaneous eyeblinks (Colzato et al. 2007b), which can be taken as a functional marker of central dopaminergic function (Blin et al. 1990; Karson 1983; Kleven and Koek 1996; Sax and Strakowski 1998; Taylor et al. 1999). The processing of stimulus–response episodes has also been found to be abnormal in Parkinson's disease OFF DA medication compared to ON DA medication, suggesting that the dorsal striatum, but not (or not so much) the ventral striatum, is driving the flexible control of retrieval of stimulus–response episodes (Colzato et al. 2012a). Indeed, as noted by Cools (2006), the dorsolateral striatum has been related to the learning and adaptation of stimulus–response (SR) "habits" (McDonald and White 1993; Reading et al. 1991; Yin et al. 2004; de Wit et al. 2011). The dorsal striatum seems to have a key role in the control of habitual actions (Balleine and O'Doherty 2010) and in representing action–outcome contingencies, which subserve adaptive goal-directed behavior across learning and memory (Grahn et al. 2008).

Finally individual differences in working memory (WM) updating have been found to predict differences in the efficiency of updating stimulus–response episodes (Colzato et al. 2012b). These latter observations are not surprising given that it is well known that striatal dopamine plays a crucial role in it. According to Moustafa et al. (2008), the nigrostriatal dopaminergic pathway serves as a gate to signal when and when not to update information in prefrontal WM. Consistent with this idea, Siessmeier et al. (2006) found that administering DA agents to healthy subjects led to a correlation between DA uptake in the striatum and BOLD activity in the dorsolateral prefrontal cortex (PFC), suggesting that the striatum might drive WM activity in the PFC. Moreover, a PET study showed that individual WM capacity predicts the striatal dopamine synthesis capacity: subjects with low WM capacity have a low synthesis capacity, while subjects with high WM capacity have a high synthesis capacity (Cools et al. 2008).

Given that the updating of stimulus–response episodes is likely to reflect the executive component of WM, we suggest that the DA nigrostriatal pathway is the most plausible candidate to mediate the updating of stimulus–response episodes. According to Grace (1991) and Floresco et al. (2003), DA in the striatum is controlled by two antagonistic processes: first, phasic DA release generated by burst firing in DA neurons and, second, constant tonic DA perpetuated by DA neuron firing. As suggested by Cools (2006), it makes sense to assume that tonic DA levels control and thus oppose phasic DA responses by stimulating autoreceptors on DA terminals, which helps to maintain a steady-state homeostasis.

In the present study, we tested this hypothesis by assessing whether the individual efficiency with which features are bound and unbound in visual perception and across vision and action can be predicted from the genetic variability associated with striatal dopaminergic functioning. In particular, we considered the polymorphism of the DAT1 gene. It is coding the dopamine transporter (DAT) responsible for DA reuptake, mainly in the striatum (Sesack et al. 1998; cf., Bertolino et al. 2006), which houses way more DATs on DA terminals than the PFC (Lewis et al. 2001). Genetic variation of the DAT1 gene is associated with individual variation in the availability of dopamine transporters and correspondently in dopamine levels. This was corroborated by positron emission tomography (PET) and by single-photon emission computed tomography (SPECT) revealing the 10-repeat allele to be associated with lower availability of striatal dopamine transporters (linked to higher dopamine levels) than the 9-repeat allele (Shumay et al. 2011; van de Giessen et al. 2009). Nevertheless, a small-sample in vivo study suggests the opposite (e.g., Heinz et al. 2000). Moreover, Bertolino et al. (2006) proposed that the 9-repeat allele of the DAT1 (much like the COMT Val allele) is associated with a selective decrease in tonic DA subcortically, thereby producing an activation of phasic DA transmission, while the 10-repeat allele (like the COMT Met allele) would increase tonic DA and decrease phasic DA subcortically. Accordingly, 9-repeat allele and 10-repeat allele of the DAT1 gene should differ with respect to the efficiency to which they handle stimulus–response bindings.

Because of the contradictory findings (Shumay et al. 2011; van de Giessen et al. 2009; Heinz et al. 2000) regarding whether 10-repeat allele or 9-repeat allele is indeed associated with lower availability of striatal dopamine transporters (linked to higher dopamine levels), the direction in which they affect stimulus–response bindings is, however, more difficult to predict. The perhaps more obvious expectation is, according to the most recent studies (Shumay et al. 2011; van de Giessen et al. 2009), that 10-repeat allele, associated with more availability of dopamine in the striatum, would show a better updating of stimulus–response bindings. Indeed, keeping in mind that (a) striatal dopamine plays a crucial role in the updating of WM, and that (b) individual differences in working memory (WM) updating have been found to predict differences in the efficiency of updating stimulus–response episodes (Colzato et al. 2012b), individuals with a predisposition for high striatal DA levels, DAT1-10/10 homozygotes, should exhibit less pronounced partial-overlap costs than 9-repeat carriers.

Moreover, given previous indications that the integration of stimulus features is likely to be mediated by muscarinic cholinergic pathways rather than dopaminergic pathways (Colzato et al. 2004, 2005), we expected that partial-overlap costs are mediated by DAT1 polymorphism for stimulus–response bindings only but not for bindings of stimulus features. Finally, hitherto, individual differences were found to mediate the management of stimulus–response bindings only for task-relevant, but not for task-irrelevant features (e.g., Hommel et al. 2011), so that we expected interactions between genetic predisposition and partial-overlap costs only for the two task-relevant features, shape and response location in our experiment.

In contrast to our hypothesis that dopamine underlies the management of stimulus–response bindings, Verguts and Notebaert (2009) have suggested that the binding of stimulus and response features into event files is mediated by phasic increases in norepinephrine (NE) triggered by the locus coeruleus. To test whether this is a possibility, we also considered the DBH5′-ins/del polymorphism, which is strongly correlated with the activity of dopamine beta-hydroxylase, the enzyme catalyzing the DA-NE conversion. The choice was driven by the fact that DBH5′-ins/del carriers are associated with an average level of plasma DBH activity, while Del/Del homozygotes and Ins/Ins homozygotes are associated with low and high levels of plasma DBH activity, respectively (Cubells et al. 2000). If, as proposed by Verguts and Notebaert (2009), NE release throughout the brain facilitates binding between task-relevant cortical areas, we should expect the individual efficiency with which features are bound and unbound in visual perception and across vision and action to be predicted by the DBH5′-ins/del polymorphism.

Methods

Participants

One hundred young healthy adults were recruited. Given that DNA samples were unobtainable from 10 participants, these adults were excluded from further analyses. The remaining 90 participants (42 male/48 female), with a mean age of 22.6 years (SD = 2.3, range 18–30) and 115.9 IQ (SD = 3.0, range 100–130), served as participants for partial fulfillment of course credit or a financial reward. The sample was drawn from adults in the Leiden and Rotterdam metropolitan area (The Netherlands), who volunteered to participate in studies of behavioral genetics. Exclusion criteria were any major medical illness that could affect brain function, current and/or past substance abuse, neurological conditions, history of head injury, and personal history of psychiatric medical treatment. Participants were selected via a phone interview using the Mini International Neuropsychiatric Interview (M.I.N.I.; Lecrubier et al. 1997). The M.I.N.I. is a well-established brief diagnostic tool in clinical and stress research that screens for several psychiatric disorders including schizophrenia, depression, mania, ADHD, and obsessive–compulsive disorder. Written informed consent was obtained from all participants after the nature of the study was explained to them; the protocol was approved by the ethical committee of the department of Psychology at Leiden University.

Apparatus, stimuli, and task

The experiment was controlled by a PC attached to a 17-inch monitor (96 dpi with a refresh rate of 120 Hz). The event-file task developed by Hommel (1998) measures binding-related effects by diagnosing *partial-repetition costs* related to (a) combinations of stimulus features (shape and color in our case) and (b) combinations of stimulus features and the response. To manipulate the repetition versus alternation of stimulus features and responses, the task comprises of pairs of trials with a prime trial (S1 → R1) followed by a probe trial (S2 → R2), see Fig. 1. The probe trial required a manual binary-choice response (R2) to the shape of the second stimulus S2 (an apple or a banana). The prime trial required a manual response (R1) to the mere onset of the first stimulus (S1). The correct R1 was signaled in advance of S1 (through a left- or right-pointing arrowhead), so that S1 and R1 could be varied independently, which was necessary to create orthogonal repetitions and alternations of stimulus shape and response. As an additional stimulus feature, color was also varied by presenting the apple or banana in green or yellow (see Colzato et al. 2006a). The standard finding obtained with this task is that the effect of repeating versus alternating stimulus features, and stimulus and response features, interacts in showing impaired performance if one feature is repeated but the other is not—the partial-overlap cost (Hommel 1998, 2004). This cost can be considered an after-effect of the just-created binding: repeating one feature retrieves the just-created event file, which corresponds to the present feature combination in the case of complete repetitions but only partially corresponds to it with partial repetitions. This creates a mismatch between retrieved and present features, which causes conflict and delays responding (Hommel 2004).

Participants were seated approximately 0.5 m from the screen. They all perform the event-file task described in the introduction and shown in Fig. 1. The task was composed of a practice block with 10 practice trials, which were not further analyzed, and an experimental block with 196 experimental trials. There were 8 conditions: Stimulus shape and color, and the response could repeat or alternate,

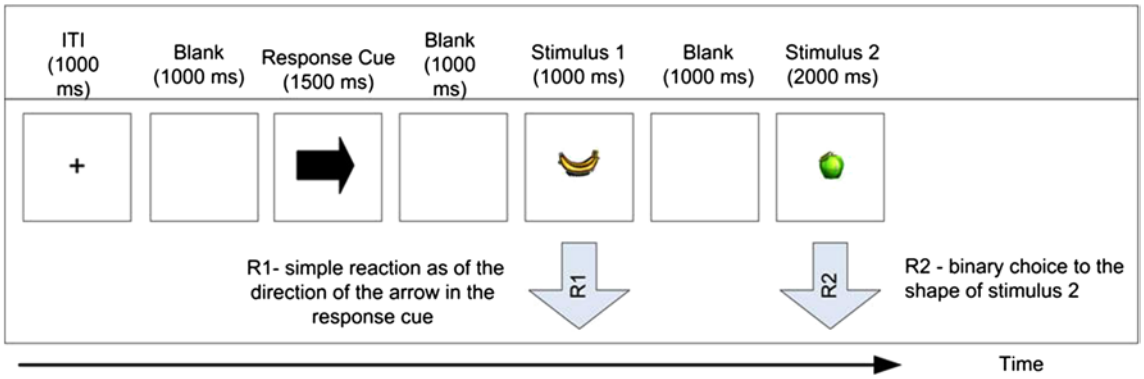

Fig. 1 Sequence of events in the event-file task. A visual response cue signaled a *left or right* response (R1) that was to be delayed until presentation of the first stimulus S1 (S1 is used as a detection signal for R1). The second stimulus S2 appeared 1,000 ms after S1. S2 signaled R2, a speeded *left or right* response according to the shape

thus creating a 2 × 2 × 2-factorial design. The order of the trials was randomized but all eight conditions appeared equally often. Half of the participants responded to the apple and the banana by pressing on the left and right key press, respectively, while the other half received the opposite mapping. The participants were asked to respond as quickly and accurately as possible.

IQ

Individual IQs were determined by means of a 30-min reasoning-based intelligence test (Raven's Standard Progressive Matrices: SPM). The SPM assesses the individual's ability to create perceptual relations and to reason by analogy independent of language and formal schooling; it is a standard, widely used test to measure Spearman's g factor as well as fluid intelligence (Raven et al. 1988).

DNA laboratory analysis

Genomic DNA was extracted from saliva samples using the OrageneTM DNA self-collection kit following the manufacturer's instructions (DNA Genotek Inc. 2006).

DAT1 gene and DBH5′-ins/del polymorphism were genotyped using PCR–RFLP techniques. Following Colzato et al. (2010), all genotypes were scored by two independent readers by comparison with sequence-verified standards.

The DAT1 polymorphism was amplified on an MJ DNA engine thermal cycler (MJ Research) with an initial denaturation at 94 °C for 4 min, followed by 32 cycles of 45 s at 94 °C, 45 s at 68 °C, and 60 s at 72 °C, and a final elongation of 5 min at 72 °C. The 25-ml reaction mixture consisted of 50 mM Tris (pH 9.0), 20 mM NH_4SO_4, 3 mM $MgCl_2$, 200 mM dNTPs, 0.5 mM primers, and 1U Taq polymerase (Invitrogen). Products were electrophoresed on 2 % agarose gel and visualized with ethidium bromide. The oligo primer sequences used to amplify the VNTR are DAT1-F: 5′-TgT ggT gTA ggg AAC ggC CTg Ag-3′ DAT1-R: 5′-CTT CCT ggA ggT CAC ggC TCA Agg, as originally described in Waldman et al. (1998).

The DBH5′-ins/del polymorphism is a 19-bp insertion–deletion located approximately 3 kb upstream of the transcriptional start codon (Nahmias et al. 1992). The following pair of primers was used (sense: 5′-GCAAAAGTCAG GCA-CATGCACC-3′, antisense: 5′-CAATAATTTGGCCT CAA-TCTTG G-3′) to amplify a PCR product of 144 bp (DBH5′-del) or 163 bp (DBH5′-ins). PCRs (final volume 10 ml) contained 10–25 ng of genomic DNA, 10 nM of each primer, 0.5 U of AmpliTaq DNA polymerase (Parkin Elmer), and 1_AmpliTaq Buffer supplied by the manufacturer. After denaturation at 94 °C for 5 min, the mixture was submitted to 30 cycles each made of 30 s denaturation (94 °C), annealing (55 °C), and elongation (72 °C).

Participants were classified by genotype as follows (see Table 1). For DAT1, two genotype groups were established: 9-repeat allele carriers and 10-repeat allele homozygotes. For DBH5′-ins/del polymorphism, three genotype groups were established: Ins/Ins allele homozygotes, Ins/Del allele heterozygotes, and Del/Del allele homozygotes.

Procedure and design

All participants were tested individually. Participants completed the SPM and subsequently performed the behavioral task.

Statistical analysis

First, repeated-measures ANOVAs were performed for analyses of age, sex, IQ differences between genotype groups. Second, the effect of each gene on the updating of visuomotor binding was assessed by means of 2 × 2 × 2

Table 1 Means of mean reaction times for responses to stimulus 2 (RT_{R2} in ms) as a function of DAT1 gene (9-repeat carriers vs. 10/10 homozygotes), DBH5′-ins/del polymorphism (Ins/Ins homozygotes vs. Ins/Del heterozygotes vs. Del/Del homozygotes), the relationship between the responses (R1 and R2), and the relationship between the stimuli features (S1 and S2) for the task-relevant feature shape. The rightmost column gives the partial-repetition costs, which differed significantly in response–shape between 9-rep carriers and 10/10 homozygotes in RTs

Significant group difference
* $p < 0.05$

Group	Response repeated		Response alternated		Partial-repetition costs
	Shape repeated	Shape alternated	Shape repeated	Shape alternated	
RTs (ms)					
DAT1 9-rep	413	482	471	430	54*
DAT1 10/10	403	459	442	417	41*
Errors (%)					
DAT1 9-rep	2.2	8.9	14.5	1.7	9.7
DAT1 10/10	1.3	7.5	11.5	1.8	7.9
RTs (ms)					
DBH Ins/Ins	389	443	435	401	44
DBH Ins/Del	419	485	465	435	48
DBH Del/Del	393	450	441	411	43
Errors (%)					
DBH Ins/Ins	1.2	10.4	14.1	2.1	10.6
DBH Ins/Del	1.8	7.9	12.9	1.7	8.6
DBH Del/Del	1.6	5.6	10.9	1.5	6.7

ANOVAs with genotype as between-subject factor and with the repetition versus alternation of response (R1 → R2), stimulus shape and color (S1 → S2) as within-participant factors. Note that statistical interactions between shape and color repetition are related to bindings of stimulus features, whereas interactions between shape and response repetition and between color and response repetition reflect stimulus–response binding (Hommel 1998). Partial-repetition costs were calculated as the difference between the reaction times (RTs) for partial repetitions (feature X repeated and feature Y alternated, or vice versa) and the RTs for complete repetitions and "complete" alternations. That is, if features X and Y repeated and alternated, their binding effect B_{XY} would be calculated as $B_{XY} = \left(RT_{X/alt,Y/rep} + RT_{X/rep,Y/alt}\right)/2 - \left(RT_{X/rep,Y/rep} + RT_{X/alt,Y/alt}\right)/2$. Binding effects thus correspond to the 2-way interaction term of the respective features (and are thus immune to possible, but theoretically less relevant, main effects of feature repetition); a value close to zero means that the repetition effects of the two given features do not interact; a value greater than zero indicates a "binding-type" interaction. A significance level of $p < .025$ ($p = .05/2$ genotypes) was adopted for all statistical tests, correcting p-values for multiple comparisons (Bonferroni correction).

Results

Participants

Genotype distribution of the DAT1 gene in our Dutch healthy population was 35 (16 male/19 female, mean age of 22.4 years, 115.8 IQ) 9-repeat carriers (38.9 %) and 55 (26 male/29 female, mean age of 22.8 years, 116.1 IQ) 10/10 homozygotes (61.1 %) and of DBH5′-ins/del polymorphism was 24 (11 male/13 female, mean age of 22.3 years, 115.9 IQ) Ins/Ins allele homozygotes (26.7 %), 43 (21 male/22 female, mean age of 22.9 years, 116.2 IQ) Ins/Del allele heterozygotes (47.8 %), and 23 (10 male/13 female, mean age of 22.6 years, 115.8 IQ) Del/Del allele homozygotes (25.5 %). The allelic distribution of the gene was in Hardy–Weinberg equilibrium ($p < 0.1$). No significant differences were found among genotype frequencies with respect to age, sex, or estimated IQ.

Experimental task

After excluding trials with missing (>1,500 ms) or anticipatory responses (<200 ms), mean reaction times (RTs) and proportions of errors (PEs) for R2 were analyzed. Table 1 provides an overview of the relevant ANOVA outcomes for RTs and PEs obtained for R2.

Replicating earlier findings (Hommel 1998; Hommel and Colzato 2004), RTs revealed significant interactions between shape and color, $F(1,91) = 7.69$, $p < 0.025$, between response and shape, $F(1,91) = 278.94$, $p < 0.025$, and response and color, $F(1,91) = 14.29$, $p < 0.025$—repeating one but not the other feature slowed down responding (423 vs. 443 ms; 405 vs. 465 ms; 430 vs. 440 ms, respectively).

The error rates followed the same pattern: response interacted with shape, $F(1,91) = 176.62$, $p < 0.025$, and color, $F(1,91) = 11.79$, $p < 0.025$. Both interactions were due to fewer errors in conditions where both features were repeated or both alternated, when compared to conditions

where one feature but not the other was repeated (1.6 vs. 12.6 %; 4.6 vs. 8.4 %, respectively).

Genetic effects

As predicted, DAT1 gene, $F(2,88) = 5.89$, $p < 0.025$, but not DBH5′-ins/del polymorphism, $F(3,88) = 1.76$, $p > 0.025$, was involved in RTs in a three-way interaction with shape and response, the two task-relevant stimulus and response features; 9-repeat carriers were more hampered (54 ms) by partial mismatches between present and previous stimulus–response relations compared to 10/10 homozygotes (41 ms). There was no hint to an interaction of shape and color repetition with DAT1 gene or DBH5′-ins/del polymorphism, $F < 1$. No further significant interactions involving the two polymorphisms were found in RTs or error rates.

Discussion

Our findings show that the DAT1, a gene coding the dopamine transporter (DAT) responsible of DA reuptake mainly in the striatum (Sesack et al. 1998), reliably predicts the individual efficiency with which features are bound and unbound across vision and action but not within visual perception. In contrast, the DBH5′-ins/del polymorphism, which is related to noradrenergic activity (Cubells et al. 2000), did not affect the magnitude of the event-file effect. Even though a null effect should be interpreted with caution, it is fair to say that our findings do not support the theory that NE is the principle neuromodulator involved in the management of stimulus–response bindings (Verguts and Notebaert 2009). Indeed, the main reason for Verguts and Notebaert to assume that NE might underlie feature integration was previous evidence for a role of NE in learning (e.g., Harley 2004). However, even though binding and learning might seem similar processes, Colzato et al. (2006b) found no relationship between them. In their study, performance was affected by both the partial overlap of stimulus features and the frequency of particular feature combinations, but partial-overlap costs did not depend on frequency, suggesting that binding and learning are independent. As pointed out by Hommel and Colzato (2009), this makes functional sense because building up enduring representations (feature-conjunction detectors) through learning should be reserved for highly reliable conjunctions only while storing arbitrary and highly variable feature conjunctions (like the shape–color combinations in our experiment or, say, combinations of particular letters and particular fonts) would be a waste of precious storage space. Nevertheless, even such arbitrary and variable feature conjunctions need to be at least temporarily integrated, which would be left to automatic and relatively criterion-free binding processes (van Dam and Hommel 2010). In any case, future studies would need to replicate our findings and examine the relationship between other polymorphisms associated with NE function and other neurotransmitters (e.g., serotonin) to further determine the specificity of striatal DA function in the updating of stimulus–response episodes—especially given that DATs on DA terminals are not restricted to the striatum but also present (though to a lesser extent) in the PFC (Lewis et al. 2001).

An important characteristic of the event-file task is that it does not require participants to maintain or recall relations between stimulus features or between stimulus and response features. When compared to more standard feature integration tasks (e.g., Allen et al. 2006; Luck and Vogel 1997), the event-file task has thus the advantage of assessing spontaneous feature integration that is unlikely to be affected or mediated by particular memory strategies. Given that participants are not required and do not benefit from maintaining and retrieving the just-created event file, after-effects of these files can be considered to index a lack of control over episodic retrieval (Kühn et al. 2011). If so, efficient controllers should show smaller after-effects (i.e., partial-overlap costs) than inefficient controllers, which fits with the observation that partial-overlap costs are reduced in individuals high in fluid intelligence (Colzato et al. 2006a) and increased in children and elderly individuals (Hommel et al. 2011). The results are also in line with the idea the stimulus–response conflict follows a U-shaped function across the lifespan (Li et al. 2009).

In view of the evidence that striatal dopaminergic pathways play a major role in the updating of WM (Moustafa et al. 2008), and given that individual differences in the efficiency of updating stimulus–response episodes are predicted by differences in WM updating (Colzato et al. 2012b), our findings further suggest that WM is involved in the handling of stimulus–response episodes but not of bindings between visual stimulus features. In principle, this involvement could be related to the creation of stimulus–response bindings, to their retrieval, or both. However, given the rather strong evidence that the creation of such bindings is much more automatic, and much less directly controlled than binding retrieval, it makes sense to relate the contribution of WM to binding retrieval. As pointed out earlier, our task does not require or benefit from the retrieval of stimulus–stimulus or stimulus–response episodes but, rather, measures spontaneous, stimulus-driven retrieval. Accordingly, the present findings suggest that 10/10 homozygotes are likely to be more efficient than 9-repeat carriers in either preventing the retrieval of currently irrelevant stimulus–response bindings and/or discounting/inhibiting such bindings upon retrieval.

Further studies will need to further explore the role of DA on the updating of episodic stimulus–response. For example, an ideal study to address this issue would be, in healthy participants, to deplete DA by means of acute tyrosine/phenylalanine depletion (ATPD). This technique has been shown to selectively decrease dopamine synthesis and release (Jaskiw and Bongiovanni 2004) and impair dopamine-dependent cognitive processes such as WM (Harmer et al. 2001; Harrison et al. 2004).

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