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Risk and protective haplotypes of the alpha-synuclein gene associated with Parkinson's disease differentially affect cognitive sequence learning

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Alpha-synuclein (SNCA) is a key factor in the regulation of dopaminergic transmission and is related to Parkinson's disease. In this study, we investigated the effects of risk and protective SNCA haplotypes associated with Parkinson's disease on cognitive sequence learning in 204 healthy volunteers. We found that the 3′-block risk SNCA haplotypes are associated with less effective stimulus-reward learning of sequences and with superior context representation of sequences. In contrast, participants with protective haplotypes exhibit better stimulus-reward learning and worse context representation, which suggest that these functions are inversely affected by risk and protective haplotypes. The Rep1 promoter polymorphism does not influence cognitive sequence learning. Because stimulus-reward learning may be mediated by the basal ganglia and context learning may be related to the medial temporal lobe, our data raise the possibility that dopaminergic signals regulated by SNCA inversely affect these memory systems.

Keywords: Alpha-synuclein, cognitive sequence learning, Parkinson's disease, reward

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Alpha-synuclein (SNCA) is a soluble presynaptic protein, which plays an important role in the uptake of dopamine into the synaptic vesicles, in membrane biogenesis and in cellular survival (Goedert 2001; Lundvig *et al.* 2005; Papapetropoulos 2006). Mutations of SNCA result in abnormal protein expression and folding, which are related to the rare familial cases of Parkinson's disease (Morris 2005).

Increasing evidence suggests that SNCA is important in the regulation of dopamine release in the mesolimbic dopamine system, including the ventral striatum/nucleus accumbens, and therefore it may influence the brain reward system (Abeliovich *et al.* 2000; Oksman *et al.* 2006; Papapetropoulos 2006). Dopaminergic neurotransmission in the brain reward system affects reinforcement learning. It has consistently been shown that the brain reward system, including the midbrain and the ventral striatum/nucleus accumbens, is activated by cognitive feedback (Aron *et al.* 2004; Rodriguez *et al.* 2006). Patients with Parkinson's disease, who have depleted dopamine in the basal ganglia, show deficits on tasks including certain types of feedback and stimulus-reward learning (Filoteo *et al.* 2005; Frank *et al.* 2004; Knowlton *et al.* 1996; Maddox & Filoteo 2001; Nagy *et al.* 2007; Shohamy *et al.* 2004, 2005, 2006; but see Swainson *et al.* 2006).

The question is therefore given: is there any effect of the genetic polymorphism of SNCA, which is a key factor in dopaminergic transmission and reward processes, on stimulus-reward learning? Mueller *et al.* (2005) identified two groups of evolutionarily related haplotypes within the 3′-region of SNCA comprising 10 single nucleotide polymorphisms (SNPs): the ancestral group was associated with increased risk of sporadic Parkinson's disease, whereas the other group of haplotypes seemed to be protective against the disease. Given that patients with Parkinson's disease show deficits on some tasks including feedback and stimulus-reward learning and that SNCA is important in dopamine-mediated reward signals, we tested the hypothesis that risk and protective haplotypes may influence feedback/reward-related and context-dependent cognitive sequence learning. We also investigated the polymorphism of the Rep1 promoter at the 5′-region of the gene, which is one of the most promising candidate genes for Parkinson's disease (Maraganore *et al.* 2006; Morris 2005).

We used a 'chaining' task during which participants were required to learn a sequence of events leading to reward (Nagy *et al.* 2007; Shohamy *et al.* 2005). Our hypothesis was that the risk haplotypes are associated with less efficient dopaminergic transmission. Therefore, we expected that participants carrying these haplotypes would show less efficient learning during the stimulus-reward learning phase but not during the context-dependent probe phase of the chaining task. In order to test the specificity of the effect of SNCA on task performance, we also used traditional measures of executive functions and sensory-motor skill learning.

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Materials and methods

Participants

Healthy volunteers were recruited from the community using newspaper advertisements and through acquaintance networks. The Mini-International Neuropsychiatric Interview was used to exclude psychopathology (Sheehan *et al.* 1998). Exclusion criteria were history of neurological or psychiatric disorders, psychoactive substance dependence and any other medical condition that can affect central nervous system functions. All participants gave written informed consent. The study was carried out in accordance with the Declaration of Helsinki.

Genotyping

Genomic DNA was extracted from venous blood samples. Ten SNPs in the 3′-region (block B) of SNCA gene were genotyped (rs356180, rs356169, rs2572323, rs356219, rs356220, rs356165, rs356204, rs3822086, rs356203 and rs356168). These SNPs show linkage disequilibrium and previously six haplotypes were identified (Mueller *et al.* 2005). Four of these haplotypes (TAGACAGCAT, CAGACAGCAT, CCGACAACAC and CAGACAACAC) are associated with decreased risk of Parkinson's disease, and two of the six haplotypes (TCAGTGACGC and CAGGTGATGC) are associated with increased risk of Parkinson's disease (Mueller *et al.* 2005). Genotyping was performed using the matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry method (Sequenom, San Diego, CA, USA). The haplotype carrier status of individual participants was determined using the Bayesian method (PHASE v2.0.2) (Stephens & Donnelly 2003). Altogether, we identified 134 cases with protective haplotypes and 70 cases with risk haplotypes (Table 1).

Six polymorphic alleles ($-2 = 263$ bp, $-1 = 265$ bp, $0 = 267$ bp, $1 = 269$ bp, $2 = 271$ bp and $3 = 273$ bp) of the Rep1 promoter region were identified, as described previously (Farrer *et al.* 2001; Xia et *al.* 2001). Polymerase chain reaction (PCR) was used to amplify the promoter region of the SNCA (8748 bp upstream of exon 1, accession no.: U46896; fluorescently tagged reverse primers: Fam 5′-CCTGGCATATTTGATTGCAA-3′ and 5′-GACTGGCCCAAGATTAACCA-3′). PCR products were treated by capillary electrophoresis and were analyzed using the GENOTYPER software (Applied Biosystems, Foster City, CA, USA).

The chaining task

The task was run on a Macintosh computer. On each trial of the experiment, the animated character (nicknamed 'Kilroy') appears in a room with three colored doors. In each room, the participant uses the computer mouse to move the cursor to click on one of the doors. If the participant's choice is incorrect, the door is 'locked' and Kilroy cannot open it. A trial consists of a full sequence of four rooms until Kilroy reaches the outside. After the learning of open doors in each room, a probe phase is introduced, during which the color of the doors is switched. For example, in room 2, Kilroy might be presented with a choice between a green door (correct in room 3) and a red door (correct in room 2). A participant who had merely learned non-sequential stimulus-response associations might choose the green door because that is a stimulus that had been directly associated with reward in the past. However, in the current context, in room 2, the green door will not be open. If the participant chooses a door that is open elsewhere in the sequence, we say that the participant committed a chaining error (for details, see Nagy *et al.* 2007; Shohamy *et al.* 2005).

Background neuropsychology

Participants received a battery including tests of executive functions/working memory [Wisconsin Card Sorting Test (Heaton 1981), verbal fluency (Benton and Hamsher 1976), Letter-Number Sequencing Test (Wechsler 1997)] and sensory-motor skill learning [mirror reading and pursuit rotor (Schmidtke *et al.* 2002)].

Data analysis

The distribution of the data was checked using Kolmogorov–Smirnov tests. Data were normally distributed. Two-tailed Student's *t*-tests were used to compare the mean number of errors from the training and probe phases of the chaining task in participants with protective and risk haplotypes. A two-way analysis of variance (ANOVA) was used to investigate the effect of haplotypes on errors in different phases of training phase (from one to four associations). In this ANOVA, risk vs. protective haplotypes were the between-subject factor, and training phase was the within-subject factor. Another two-way ANOVA was used to investigate the effect of haplotypes on errors in the training phase and in the probe phase. In this ANOVA, risk vs. protective

Table 1: Demographical and neuropsychological characteristics of the participants carrying protective and risk haplotypes of the *SNCA* gene

	Protective haplotypes ($n = 134$)	Risk haplotypes ($n = 70$)
Age (years)	36.8 (9.6)	34.7 (8.2)
Gender (male/female)	66/68	32/38
Education (years)	14.8 (3.9)	16.4 (6.0)
Wisconsin Card Sorting Test, number of categories	5.3 (1.2)	5.4 (1.7)
Wisconsin Card Sorting Test, number of perseverative errors	10.5 (6.8)	10.2 (7.4)
Verbal fluency	41.5 (10.6)	42.9 (11.1)
Letter-Number Sequencing Test	9.8 (2.3)	9.7 (2.1)
Mirror reading (1st trial/3rd trial, second)	413.5 (252.9)/206.3 (168.4)	408.5 (239.0)/208.3 (174.3)
Pursuit rotor (time off target, 1st to 3rd trial/4th to 6th trial)	21.6 (12.8)/16.1 (9.1)	18.6 (14.5)/12.2 (8.2)

Data are mean (SD). Student's *t*-test revealed no significant differences between participants with risk and protective haplotypes ($P > 0.1$).

haplotypes were the between-subject factor and training vs. probe phase was the within-subject factor. Student's *t*-tests were used for post-hoc analysis and for the analysis of background neuropsychological measures. Pearson's product moment correlation coefficients were calculated between errors in the chaining task and background neuropsychological measures. The level of significance was set at alpha <0.05.

Results

Figure 1 shows the number of errors in the training phase (stimulus-reward learning of the chaining sequence) and in the probe phase (context changes). Participants with 3′-block risk haplotypes committed more cumulative errors during the training phase (mean number of errors: 2.3, SD = 1.7) compared with participants carrying protective haplotypes (mean number of errors: 1.6, SD = 0.8) [$t(199) = -3.81$, $P < 0.001$]. As the length of the sequence increased (from phase 1 to phase 4), the mean number of errors also increased [main effect of phase: $F(3,597) = 20.96$, $P < 0.001$]. The effect of haplotypes was also significant [$F(1,199) = 14.55$, $P < 0.001$]. Participants with risk haplotypes committed more errors in phases 2, 3 and 4 compared with participants carrying protective haplotypes ($t > 2.4$, $P < 0.05$) (Fig. 2).

In the probe phase, participants with protective haplotypes performed worse (mean number of errors: 2.3, SD = 2.6) than participants with risk haplotypes (mean number of errors: 1.5, SD = 2.0) [$t(195) = 2.30$, $P < 0.05$; ANOVA interaction between haplotypes (protective vs. risk) and task phase (training vs. probe): $F(1,195) = 14.74$, $P < 0.001$) (Fig. 1).

The percentage of chaining errors was 70.5% (SD = 58.6) in the case of participants with risk haplotypes, whereas this value was 81.9% (SD = 47.4) in the case of participants with protective haplotypes ($P > 0.1$). This indicates a tendency for participants with protective haplotypes to choose previously correct doors but to choose them at the wrong point in the chain. However, because of the large standard deviations, the difference did not reach the level of statistical significance.

There were no significant differences between male and female participants, and there was no gender by haplotypes by task phase interaction ($P > 0.1$). There was no significant correlation between age and performance in the training phase (participants with protective haplotypes: $r = 0.02$ and participants with risk haplotypes: $r = 0.11$) and in the probe phase (participants with protective haplotypes: $r = 0.09$ and participants with risk haplotypes: $r = 0.08$). Participants with protective and risk haplotypes did not differ in Wisconsin Card Sorting Test, verbal fluency, mirror reading and pursuit rotor (Table 1).

We found no significant correlations between errors in the training or probe phase of the chaining task and background neuropsychological measures ($r < 0.2$).

The distribution of the six polymorphic variants of the Rep1 promoter region is shown in Table 2. ANOVAs revealed that

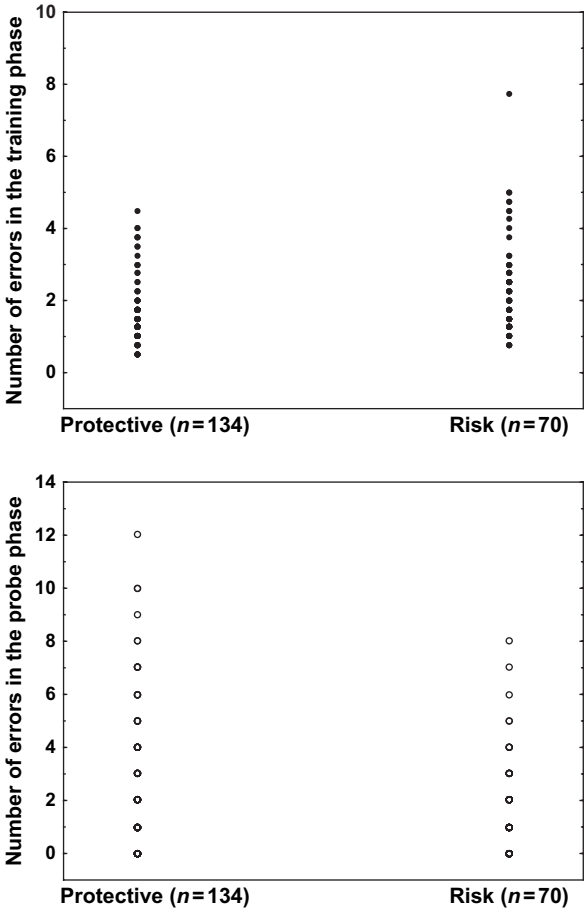

Figure 1: Errors as a function of SNCA haplotypes. Scatter plot of errors in the training phase (filled symbols) and in the probe phase (open symbols) in participants with protective and risk haplotypes.

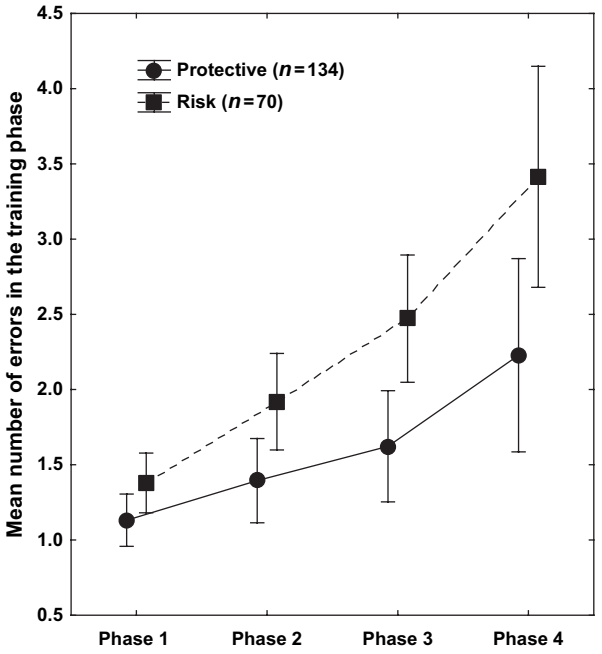

Figure 2: Mean number of errors in the training phase (stimulus-reward learning). Error bars indicate 95% confidence intervals.

Table 2: The effect of Rep1 polymorphism on cognitive sequence learning

	Polymorphic alleles					
	−2 (263 bp)	−1 (265 bp)	0 (267 bp)	1 (269 bp)	2 (271 bp)	3 (273 bp)
Percentage of participants	0	2.0	40.2	51.5	5.9	0.5
Mean number of errors, training phase	—	1.9 (SD = 1.2)	1.7 (SD = 0.9)	1.5 (SD = 1.0)	1.7 (SD = 1.2)	1.8 (SD = 1.5)
Mean number of errors, probe phase	—	2.0 (SD = 2.4)	1.9 (SD = 1.7)	1.9 (SD = 2.1)	1.9 (SD = 2.0)	1.8 (SD = 1.8)

these polymorphic variants had no significant effect on the number of errors in the training phase and in the probe phase ($F < 1$, $P > 0.5$).

Discussion

The data presented in this article suggest a double dissociation between stimulus-reward and context-dependent cognitive sequence learning in participants with risk and protective haplotypes of SNCA associated with Parkinson's disease. Participants with risk haplotypes exhibited less efficient stimulus-reward learning, which is similar to that found in patients with unmedicated Parkinson's disease (Nagy *et al.* 2007; Shohamy *et al.* 2005), but in the patients, inefficient learning was much more pronounced than in healthy volunteers with risk haplotypes. Because L-DOPA improved stimulus-reward learning of chaining sequences in patients with Parkinson's disease (Shohamy *et al.* 2005), it is plausible to hypothesize that the risk haplotypes of SNCA are associated with decreased dopaminergic transmission in the basal ganglia.

A more unexpected and intriguing finding was that the risk haplotypes were associated with *better* performance during the context-dependent phase of the chaining task. After the learning of the chain of associations (the color of open door in each room), the colors of the incorrect doors were switched such that in each room, in addition to the correct door of that room, there also appeared a door that was the correct door elsewhere in the sequence. Thus, for example in room 4, the participant might be presented with a choice between a green door (correct) and a red door (incorrect in room 4 but correct in room 3). The probe phase was designed to verify that participants learned the correct door in its correct place in the sequence.

Because the context-dependent phase of sequence learning may be related to the medial temporal lobe, including the hippocampus, the issue is how SNCA and dopaminergic signals may affect the functioning of neurons of this brain structure. Dopaminergic pathways also exist in the medial temporal lobe where they appear to modulate prefrontal–medial temporal lobe interactions (Poldrack & Rodriguez 2004). Intriguingly, hippocampal activity is associated with positive feedback during classification learning (Seger & Cincotta 2005). According to Lisman and Otmakhova (2001), the dentate and CA3 hippocampal regions could store and recall memory sequences in context. These authors showed that dopamine reduces the direct cortical input to CA1 while having little effect on the CA3 region, which is important in sequence and context learning. Therefore, it is possible that SNCA has an important effect on the interaction between CA3 and CA1 regions by the modulation of dopaminergic transmission. This may result in altered storage and recall memory sequences in context.

Results also revealed that the risk haplotypes did not affect working memory/executive functions and sensory-motor skill learning. This is consistent with previous neuropsychological data suggesting that cognitive skill and habit learning can be independent of executive functions and sensory-motor skill learning (e.g. Daum *et al.* 1995; Knowlton *et al.* 1996; Saint-Cyr *et al.* 1988; Schmidtke *et al.* 2002; Weickert *et al.* 2002). Contrary to this view, one may assume that dopamine in the dorsolateral prefrontal cortex and in its associated striatal regions is essential for working memory functions that may participate in the mnemonic maintenance of 'chains' of associations, in the monitoring of actions and their consequences and in correct context representation. However, we did not find correlation between performance on executive tests and performance on the stimulus-reward learning and context-dependent phase of the chaining task. Given that during the training phase participants received many trials, the task was overtrained, which minimized the role executive functions and working memory have in the intentional monitoring of action–outcome associations, and therefore the formation of stimulus-response habits could easily be obtained (Yin & Knowlton 2006).

We also investigated the Rep1 promoter polymorphism, which may have a significant effect on gene expression (Chiba-Falek & Nussbaum 2001) and is associated with Parkinson's disease (Maraganore *et al.* 2006). However, this polymorphism had no effect on chaining task performance. The reason for this negative finding is not clear. It is possible that the effect of the Rep1 promoter polymorphism on gene expression does not lead to significant changes in neuronal functions that may produce alterations in cognitive sequence learning. In addition, the *in vivo* effects of the Rep1 polymorphism on gene expression are not fully characterized. It does not necessarily mean, however, that this polymorphism is not associated with the risk of Parkinson's disease.

An important limitation is that it is unknown how 3′-block SNCA haplotypes affect protein functions and how they can increase or decrease the risk for Parkinson's disease. A splice variant of SNCA (NACP112) lacks exon 5 (Ueda *et al.* 1994), which is located within the investigated 3′-block haplotypes.

This could determine the expression of the splice variant, leading to altered dopaminergic transmission and reward sensitivity. Regardless of the mechanism of action, it is somewhat unexpected that risk haplotypes for Parkinson's disease influence cognitive sequence learning, given that for a long time it has been postulated that in this disease, motor functions are first affected. For example, Buhmann *et al.* (2005) showed motor reorganization in asymptomatic carriers of a mutant *Parkin* allele, providing a model for presymptomatic parkinsonism. The presymptomatic period can last as long as 5 years (Fearnley & Lees 1991), during which neuronal compensation develops to adapt to gradually declining striatal functions. It is unknown how risk and protective haplotypes of SNCA influence fine motor functions and their brain correlates in the presymptomatic stage of Parkinson's disease. However, SNCA haplotypes had no significant effects on performances on the sensory-motor tasks used in this study. Further studies should clarify this issue by comparing cognitive sequence learning and motor tasks in asymptomatic carriers with risk/protective variants of SNCA in order to assess latent striatal dysfunctions and neuronal adaptation to it. To achieve this aim, four steps should be taken. First, the functional effects of genetic variants of SNCA should be identified at the cellular and synaptic level. Second, these changes should be correlated with behavioral parameters. In this respect, it is critical to elucidate how different genetic variants may modulate sensitivity for positive and negative feedback. Third, using functional imaging techniques, brain activation patterns associated with different genetic variants should be identified, with a special reference to different regions of the basal ganglia, medial temporal lobe and frontal lobe. Finally, it should be determined how these subtle changes contribute to the risk of Parkinson's disease, when they first appear during the presymptomatic period, how they interact with environmental factors and how these measures can be used for the early recognition of the disease.

In conclusion, this is the first study to show that risk and protective variants of SNCA associated with Parkinson's disease affect cognitive sequence learning. We showed an intriguing and unexpected double dissociation: haplotypes associated with increased risk of Parkinson's disease resulted in less efficient stimulus-response learning but with more efficient context representation. This unique double dissociation suggests that certain genetic variants that adversely affect particular learning functions may have a positive effect on other cognitive domains.

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