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Associations between genetic variations and global motion perception

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Abstract

The cholinergic system is known to strongly modulate perceptual and cognitive processes, and the alpha7 subunit of the cholinergic nicotinic receptor (CHRNA7) is broadly expressed within the visual system. Here, we assessed whether genetic variations of CHRNA7 affect coherent motion perception. Motion perception has been shown to decline with age, and it has previously been suggested that the effects of genetic variations are magnified by age. Therefore, we tested both older ($n = 62$) and younger adults ($n = 63$). We found that motion coherence thresholds were significantly higher for older compared to younger adults, which is in accordance with previous studies. Interestingly, there was a strong relationship between variants of the SNP rs2337980 of the CHRNA7 and motion direction discrimination. In particular, participants carrying the TC genotype had considerably lower motion coherence thresholds than CC carriers. The effect of genotype did not interact with age. Our results show that genetic variations are associated with perceptual performance, but are unlikely to explain age-related changes.

Keywords Coherent motion · Genetic variations · Cholinergic system · CHRNA7 · Aging

Introduction

Visual perception is strongly influenced by acetylcholine. For example, studies in macaque monkeys have demonstrated that the cholinergic system up- and down-regulates the incoming visual information in the primary visual cortex (Disney et al. 2007) and enhances visual perception (Kang et al. 2014). Increasing acetylcholine by the cholinesterase inhibitor donepezil improves perceptual

learning in humans (Rokem and Silver 2010). In addition, visual backward masking is impaired after nicotine deprivation in chronic smokers, suggesting a strong link between nicotine levels and visual temporal processing (De Leon and Diaz 2005; Leonard et al. 2007; Kunchulia et al. 2014). The alpha7 subunit of the cholinergic nicotinic receptor gene (CHRNA7) is of particular importance with regards to perception, because it is broadly expressed in the visual system including the retina and the primary visual cortex (V1; Aztiria et al. 2004; Gotti et al. 2007; Galvin et al. 2018). In addition, visual acuity is reduced in alpha 7 nicotinic receptor knockout mice (Origlia et al. 2012). Genetic alternations of $\alpha 7$ -nAChR have been reported in a variety of disorders such as schizophrenia (Severance and Yolken 2008), autism spectrum disorder (Deutsch et al. 2011), and Alzheimer's disease (Parri et al. 2011). These disorders are all accompanied by substantial deficits in visual perception (Chen et al. 2003; Spencer et al. 2013; Koldewyn et al. 2010; Robertson et al. 2014; Fernandez et al. 2013). Given the broad expression of the $\alpha 7$ -nAChR in the visual system, it is reasonable to assume a relationship between these genetic alterations and deficits in visual perception. Despite CHRNA7 being an attractive candidate for investigating the relationship

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between common genetic variations and visual perception, its relationship with visual perception in humans has rarely been studied. Bakanidze et al. (2013) found that a single-nucleotide polymorphism (SNP) of the CHRNA7 correlates with visual backward masking deficits in schizophrenic patients. Up to date, however, no studies have investigated possible correlations between genetic variations of CHRNA7 and visual perception in the healthy population, a link that would emphasize its importance in visual perceptual functions in mental disorders and potentially help to intervene at an early stage of the disease.

Here, we tested whether SNPs of the CHRNA7 play a role in motion perception in neurotypical healthy adults. Motion perception is a fundamental part of visual perception that allows us to discriminate the movement of objects in the world around us (Hutchinson et al. 2014). Motion perception starts in retinal ganglion cells that project to the lateral geniculate nucleus (LGN), in particular the magnocellular system for motion perception (Maunsell et al. 1990, see also Billino and Pilz 2019). The LGN projects further to neurons in the primary visual area (V1). Global motion is processed in the middle temporal area (hMT/V5), which receives direct connections from V1 and indirect ones via V2 and V3 (McCool and Britten 2008). We included younger and older participants in our study, because it has been suggested that the effects of common genetic variations on cognitive functions are magnified by age, thus, increasing inter-individual differences (Papenberg et al. 2015a, b). In addition, visual motion perception is the most studied perceptual ability in healthy aging and, therefore, can be used as a conceptual model for studying perceptual aging (see Billino and Pilz 2019, for a review). It has been shown that older adults are worse than younger adults at detecting, discriminating, and identifying the direction of global motion in random-dot kinematograms (Ball and Sekuler 1986; Bennett et al. 2007; Billino et al. 2008; Hutchinson et al. 2012, 2014; Tran et al. 1998; Trick and Silverman 1991). However, large individual differences in performance exist within the group of older adults in that some older participants perform on the level of younger adults, whereas others show large deficits in performance (e.g., Billino et al. 2009; Norman et al. 2013; Pilz et al. 2015, 2017; Shaqiri et al. 2015; Shain and Norman 2018). The magnitude of the age-related deficit strongly depends on stimulus parameters such as speed (Snowden and Kavanagh 2006), motion coherence (Pilz et al. 2017), motion direction (Pilz et al. 2017; Shain and Norman 2018) and contrast (Allen et al. 2010), factors that affect performance on an individual level. These individual differences suggest that age alone cannot explain age-related deficits in motion perception. Given that cognitive effects of common genetic variations are magnified by age (Papenberg et al. 2015a, b), it is possible that individual differences in motion perception are related to genetic variations.

Methods

Participants

Participants were 125 adults, including 63 younger adults ranging from 18 to 29 years (M 22.5, SD 2.99) and 62 older adults ranging from 60 to 75 years (M 64.5, SD 3.56). Participants were recruited from the general population. All participants completed a questionnaire related to general health and their history of psychiatric disorders including schizophrenia. None of the participants reported any current health issues. All participants were Georgian. For the genetic analysis, each participant donated 20 ml of blood. Prior to the behavioral experiment, we determined visual acuity for each participant with the Freiburg visual acuity test (FrACT, Bach 1996). One hundred and six participants (60 young/46 old) had normal or corrected-to-normal vision of 0.8 or above (M 1.39, SD 0.35). Three younger and 16 older adults had a visual acuity below 0.8 and their data were excluded from final analysis. Hence, the final sample was composed of 106 participants. The demographic characteristics of the sample are shown in Table 1.

The study was approved by the Bioethics Committee of the Ivane Beritashvili Center of Experimental Biomedicine and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Apparatus and stimuli

Stimuli were presented on a Samsung SyncMaster 957DF CRT screen with a 100-Hz refresh rate and a resolution of 1024×768 pixels. Stimulus luminance was 100 cd/m^2 as measured with a GretagMacbeth Eye-One Display 2 colorimeter. The background luminance of the screen was below 1 cd/m^2 .

Stimuli were random dot kinematograms consisting of a field of 50 white dots moving at a speed of $5.6^\circ/\text{s}$. The dots

Table 1 Demographic characteristics of groups genotyped for a single-nucleotide polymorphism (SNP) [rs2337980] of the CHRNA7

Genotype	<i>N</i>	Age Old/young	Sex F/M
CC	40	<i>M</i> 38.93 <i>SD</i> 21.24 15/25	22/18
TC	49	<i>M</i> 41.63 <i>SD</i> 21.83 23/26	28/21
TT	17	<i>M</i> 42 <i>SD</i> 20.9 8/9	9/8

were presented on a black background within a rectangular region ($8.9^\circ \times 6.7^\circ$) in the middle of the screen and had a size of $5'$. The target dots moved coherently either to the right or to the left, while the distractor dots were allocated a random direction at the beginning of each trial. Trials were separated by an interval of 500 ms.

The lifetime of the dots was not limited. A dot moving out of the rectangular region reappeared at a new random position within the region and continued moving in the same direction that it had been allocated at the beginning of the trial. A red fixation dot with a size of $8'$ appeared 500 ms before each trial and remained on the screen for the entire stimulus presentation (Fig. 1).

Procedure

Participants were seated 200 cm away from the screen in a dimly lit room and had to indicate whether the global motion of the dots was either to the right or left by pushing a button in their right or left hand, respectively. Auditory feedback was provided. Motion coherence, i.e., the percentage of target dots, varied randomly according to a PEST procedure (Creelman and Taylor 1969) with a starting value of 20% coherence. We determined the motion coherence threshold at 75% correct for each participant. Each participant completed 120 trials.

Genotyping

DNA was extracted from blood lymphocytes ($N = 125$) using a blood and tissue kit (Qiagen) according to the manufacturer's instructions. Forward and reverse primers 5'-CTG TCCTCCGGTATCTGTG-3'; 5'-CAGTCACTTCTGTGT CTAAG-3' were used for amplification of relevant DNA regions by polymerase chain reaction (PCR) (Bakanidze

et al. 2013). Amplification of genome fragments was carried out using Platinum PCR SuperMix reagents (Invitrogen) and GenAmp PCR System 9700 (Applied Biosystems). Primers were diluted to a $5\ \mu\text{M}$ working concentration. PCR profile: 94°C for 5 min; a touchdown of 35 cycles of 94°C for 1 min, 56°C for 1 min, 72°C for 1 min, followed by a final extension at 72°C for 7 min. An aliquot of $5\ \mu\text{L}$ from each PCR was run on a 1% agarose gel to visualize the DNA fragments by SYBRSafe staining. An ExoSAP-IT cleanup reagent was used for enzymatic cleanup of the amplified PCR product. Single-stranded sequencing of purified amplicons was performed with the primers of the PCR on the ABI capillary sequencer 3130xl (Applied Biosystems) using a BigDye Terminator, version 3.1 sequencing kit. PCR fragments were sequenced in both directions to assure sequence accuracy. Analysis of the sequencing data was carried out using Geneious v10.1.3. software; the alignment of the sequences was performed with BioEdit v7.2.

Based on a previous study by Bakanidze et al. (2013), we first targeted three SNPs, namely [rs3826029] [rs2337506] [rs2337980] of CHRNA7. A single-nucleotide polymorphism (SNP) [rs2337506] of the CHRNA7 was genotyped for 47 subjects out of 125 participants (25 older and 22 younger; 16 GG allele carriers, 2 AA allele carriers, and 29 AG allele carriers). Since the number of AA allele carriers was very small, in a preliminary analysis, homozygotes rs2337506 GG carriers were compared with all A-allele carriers. We did not find an interaction between SNP rs2337506 with motion direction discrimination, $F(1,43) = 1.27$, $p = 0.265$. The blood of 49 participants was genotyped for SNP rs3826029 (25 older and 24 younger; 25 CC allele carriers, 2 TT allele carriers, and 22 TC allele carriers). Given that the number of TT allele carriers was very small, we contrasted homozygotes rs3826029 CC with all T-allele carriers and did not find an interaction between SNP rs3826029 and

Fig. 1 Example of a trial structure. Each trial began with a presentation of the red fixation dot (**a**). **b** White dots stimuli. Target dots moved coherently to the right or to the left, while distractor dots moved randomly. Central red fixation dot was maintained during

stimuli presentation. The trials were separated by inter-trial interval (ITI) of 500 ms (**c**). Participants had to indicate left or right moving direction of target dots

motion direction discrimination, $F(1,45) = 0.03$, $p = 0.863$. However, a preliminary analysis of the data from 51 participants related to SNP rs2337980 showed a significant interaction between genetic variations of SNP rs2337980 with performance of the motion direction discrimination, $F(1,47) = 7.59$, $p = 0.008$ (25 older and 26 younger; 23 CC allele carriers, 3 TT allele carriers and 25 TC allele carriers; CC allele carriers were contrasted with all T alleles). Based on these results, we focused our study on SNP rs2337980.

Genotyping was carried out at the Genome Center, National Center for Disease control and Public Health, Tbilisi, Georgia. Allele frequencies were 0.59 for the C-allele and for 0.41 the T allele. There were 43 C-allele homozygotes, 62 heterozygotes, and 20 T-allele homozygotes. The observed genotype frequencies were consistent with the Hardy–Weinberg equilibrium ($X^2 = 0.09$, $p > 0.05$) determined by the Hardy–Weinberg equilibrium calculator (<http://www.oege.org/software/hwe-mr-calc.shtml>; Rodriguez et al. 2009).

Results

We conducted an analysis of variance (ANOVA) on motion coherence thresholds with between-subject factors Genotype (CC/CT/TT) and Age group (old/young). In addition, we used bootstrapping to test the significance of the obtained effects (Efron and Tibshirani 1994). One thousand resampled data sets were used for calculating a bias-corrected and accelerated (BCa) confidence interval. We used SPSS for the statistical analyses (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp).

Fig. 2 Mean motion coherence thresholds for CC, TT, and TC carriers for all participants, for older and younger participants. The thresholds are plotted as the percentage of target dots. Errors bars show standard errors of the mean. Participants carrying the TC genotype performed the task significantly better than CC carriers. Older adults had higher motion coherence thresholds than younger ones

The 3 (Genotype) $\times$ 2 (Age Group) ANOVA showed a main effect of Age Group $F(1, 100) = 37.23$, $p < 0.001$, $\eta_p^2 = .27$, older adults had higher motion coherence thresholds ($M 29.64$, $SE 1.4$) than younger adults ($M 18.14$, $SE 1.26$); and a main effect of Genotype $F(2, 100) = 4.47$, $p = 0.014$, $\eta_p^2 = 0.08$ (Fig. 2; Table 2). Post hoc tests with Tukey's HSD confirmed lower motion coherence thresholds for TC-allele carriers compared to CC carriers $p = 0.057$, Cliff's $\delta = 0.26$. There were no significant differences either between the TC and TT carriers $p = 0.281$, Cliff's $\delta = -0.15$, or between TT and CC carriers $p = 0.973$, Cliff's $\delta = 0.06$.

Table 3 shows the mean differences between Genotypes based on 1000 bootstrap samples. There was no interaction between age group and genotype $F(2, 100) = 2.06$, $p = 0.133$, $\eta_p^2 = 0.04$ (Fig. 2).

Discussion

We recently showed that genetic changes in the cholinergic nicotinic receptor alpha 7 subunit (CHRNA7) correlate with masking deficits in schizophrenic patients (Bakanidze et al. 2013), which we attributed to deficient neuromodulation of the cholinergic system (Herzog and Brand 2015). In particular, a single-nucleotide polymorphisms of CHRNA7 was correlated with masking performance. Here, we targeted one out of the five SNPs that were tested in the previous study on schizophrenia, namely [rs2337980] of CHRNA7, and assessed whether variations in this SNP can explain

Table 2 Estimated marginal means of motion coherence thresholds for the genotype groups with BCa 95% confidence interval based on 1000 bootstrap samples

Genotype	Mean	95% CI range on based 1000 bootstrap samples
CC	<i>M</i> 26.201 SE 1.417	23.215–29.095
TC	<i>M</i> 20.726 SE 1.242	18.342–22.929
TT	<i>M</i> 24.74 SE 2.242	20.375–28.835

Table 3 Mean differences in motion coherence thresholds between genotype groups based on 1000 bootstrap samples

Genotype	Mean differences	95% CI range on based 1000 bootstrap samples
CC-TC	4.3	0.44 to 8.57
CC-TT	0.56	– 5.06 to 6.47
TT-TC	3.73	– 2.64 to 10.41

individual differences in motion direction discrimination in healthy aging.

In accordance with previous studies, older adults had significantly higher motion coherence thresholds than younger adults (Ball and Sekuler 1986; Bennett et al. 2007; Billino et al. 2008; Tran et al. 1998; Trick and Silverman 1991). In addition, we found a strong association of SNP rs2337980 of the CHRNA7 with motion direction discrimination. In particular, participants carrying the TC genotype performed significantly better than CC carriers, i.e., they had lower motion coherence thresholds. Surprisingly, however, we only found an overall effect of genotype but no age-related differences, i.e., both younger and older adults were equally affected by variations in the SNP. Interestingly, previous studies have reported that CC carriers in SNP rs2337980 of the CHRNA7 perform worse in tasks related to response-inhibition (Rigbi et al. 2008), and show an increased benefit of nicotine for task performance compared to TC/TT carriers (Rigbi et al. 2011). These results suggest that the CC variant in SNP rs2337980 is a disadvantageous genotype for some cognitive and perceptual functions, including motion perception.

Age-related changes in the cholinergic system affect cognition (see Dumas and Newhouse 2011) and visual processing (Ricciardi et al. 2009). However, age-related changes are unlikely to relate to variations of a single gene, but rather relate to complex interactions between multiple genes (Kedmi and Orr-Urtreger 2011). Therefore, further studies are needed to explore interactive effects of multiple genes within the cholinergic system to understand the involvement of the cholinergic system in motion perception with regards to healthy aging.

Based on the resource modulation hypothesis, which postulates that genetic effects on cognition are more pronounced in individuals with limited neuroanatomical or neurochemical resources (Lindenberger et al. 2008; Li et al. 2017), we expected the relationship between variations of CHRNA7 and motion perception to be more pronounced in older adults. However, despite increased motion coherence thresholds for older adults and an apparent relationship between motion coherence and genetic variations in SNP rs2337980 of the CHRNA7, we did not find a relationship between age-related decline and genetic alterations.

The absence of an interaction between age group and genotype suggests that a genetic predisposition does not contribute to the inter-individual differences in motion perception of older people, and it is possible that age-related changes are related to visual experience rather than genetic differences. Our results provide an important piece in the puzzle of understanding the underlying mechanisms of age-related changes in visual perception. However, it is important to note that we only studied two age groups and focused only on one SNP. Therefore, further studies are necessary to

explore age-related associations between motion direction discrimination and genotypes across the age range, assessing other important SNPs.

In conclusion, our results support previous findings of age-related decline in motion perception. More importantly, we found a relationship between motion coherence and a genetic variation of the CHRNA7, indicating a strong relationship between the nicotinic system and motion perception that is independent of age.

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