A functional genetic variation of the 5-HT2a receptor affects human memory

Dominique J-F de Quervain, Katharina Henke, Amanda Aerni, Daniel Coluccia, M Axel Wollmer, Christoph Hock, Roger M Nitsch & Andreas Papassotiropoulos

Human memory capacity is highly variable across individuals and is influenced by both genetic and environmental factors. A roughly 50% heritability estimate[1] indicates that naturally occurring genetic variations have an important impact on this cognitive ability. Therefore, we investigated a functional variation of a memory-related serotonin receptor in 349 healthy young volunteers, and found 21% poorer memory performance in subjects with the rare variant.

Serotonin (5-hydroxytryptamine or 5-HT) and its receptors, including the 5-HT2a receptor, are important for learning and memory[2]. 5-HT2a receptors are distributed throughout the human central nervous system, including the hippocampus and the prefrontal cortex[3], which are important brain structures for memory[4]. Drugs with high affinity to the 5-HT2a receptor modulate memory formation in rats[5]. A frequent polymorphism of the gene encoding the 5-HT2a receptor (*HTR2A*) predicts an amino acid substitution (His to Tyr) at residue 452 (H452Y) and shows a minor-allele frequency of about 9% (ref. 6). Compared with carriers of the common His/His variant, heterozygous (His/Tyr) carriers show a blunted receptor response, as measured by amplitude and timing of intracellular calcium mobilization upon pharmacological stimulation[7,8].

We investigated the effects of the H452Y polymorphism on human memory. To control for type-I statistical error and for effects of educational level on memory, we recruited two independent populations of either university students (academic group) or age-matched employees/trainees who were not studying at the university and did not have a university degree (non-academic group). Subjects gave written informed consent to participate in the study, and the experiments were approved by the ethics committee of the University of Zürich, Switzerland. All subjects underwent cognitive assessment during two consecutive days. On the first day, subjects viewed six sets of semantically unrelated nouns (five nouns per set) presented at a rate of 1 word per second with the instruction to learn the words for immediate free recall after each series. In addition, subjects underwent an unexpected delayed free recall test of the learned words after 5 min and again after 24 h. Both delayed recall tests reflect episodic memory[4]. In contrast to the 5-min recall, the 24-h recall additionally requires successful protein synthesis–dependent memory consolidation[9].

The 5-HT2a genotype exerted a significant influence on the delayed free recall of words after 5 min, with His/Tyr subjects showing 21% poorer memory performance compared to His/His subjects (**Fig. 1**). This effect of genotype was observed in both the academic and non-academic groups (academics: His/His, 9.2 ± 0.3 (mean ± s.e.m.); His/Tyr, 7.9 ± 0.5; $F = 4.9$; d.f. = 1; $P = 0.03$; non-academics: His/His, 8.2 ± 0.3; His/Tyr, 5.7 ± 1.0; $F = 4.9$; d.f. = 1; $P = 0.03$; combined: His/His, 8.7 ± 0.2; His/Tyr, 6.9 ± 0.6; $F = 9.3$; d.f. = 1; $P = 0.002$) and was independent of gender and age. In addition, a genotype distribution analysis after median split for the 5-min recall performance revealed a significantly higher proportion of His/Tyr subjects in the population with poorer memory performance (*i.e.*, equal to or below the median of 8 recalled words, $P < 0.001$, **Table 1**). The genotype-dependent difference was maintained but not increased after 24 h (**Fig. 1**), suggesting that the H452Y polymorphism did not additionally influence protein synthesis–dependent memory consolidation. Immediate free recall was not affected by the 5-HT2a genotype (**Fig. 1**).

In addition to the verbal memory test, subjects performed a modified version of the Rey-15-figures free-recall test[10], which included the presentation of 15 figures in sequence—each figure for 2 s—with the instruction to learn them for immediate recall. In addition, subjects underwent an unexpected delayed free recall test

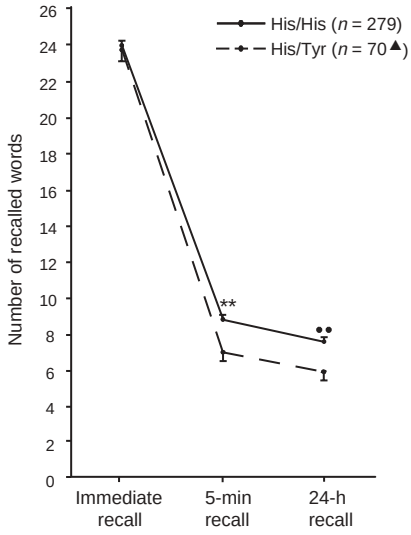

Figure 1 Effect of the 5-HT2a H452Y genotype on verbal memory in young healthy human subjects. Whereas immediate recall performance was unaffected by the 5-HT2a genotype ($F = 0.1$; d.f. = 1; $P = 0.73$), genotype significantly influenced delayed free recall of words, both 5 min ($F = 9.3$, d.f. = 1, $^{**}P = 0.002$) and 24 h ($F = 8.0$, d.f. = 1, $^{••}P = 0.005$) after word presentation. The number of recalled words 5 min after presentation was also significantly affected by education level (academics, 8.6 ± 0.3; non-academics, 6.9 ± 0.5; $F = 8.6$; d.f. = 1; $P = 0.004$), gender (females, 8.7 ± 0.3; males, 6.8 ± 0.5; $F = 10.7$; d.f. = 1; $P = 0.001$) and age (negative influence of increasing age; $F = 5.2$, d.f. = 1, $P = 0.02$). Educational level, gender and age exerted similar significant effects on the 24-h recall. Memory testing and genotyping was done in a total of 349 young healthy human subjects (243 females, 106 males; 230 academics, 119 non-academics; mean age 22 years, range 18–35 years). For statistical evaluation, we used a multifactorial analysis of covariance controlling for age, gender and education. For the analysis of delayed recall, we additionally included immediate recall performance as a covariate. ▲, one subject was Tyr homozygous and was included in the heterozygous group for statistical analysis. Error bars represent s.e.m.

Division of Psychiatry Research, University of Zürich, Lenggstr. 31, 8029 Zürich, Switzerland. Correspondence should be addressed to D.Q. (quervain@bli.unizh.ch) or A.P. (papas@bli.unizh.ch).

Published online 19 October 2003; doi:10.1038/nn1146

Table 1 Distribution of genotypes after median split: 5-min recall performance

	≤8 words recalled (n = 166)	>8 words recalled (n = 183)
His/His	73%	86%
His/Tyr	27%	14%

χ^2 = 11.0, d.f. = 1, P < 0.001 adjusted for immediate recall performance, age, sex and education.

of the learned figures 5 min and again 24 h after presentation. In male subjects, the genotype did not significantly affect immediate recall (His/His, 7.2 ± 0.2; His/Tyr, 7.1 ± 0.7; F = 0.007; d.f. = 1; P = 0.93), but it significantly influenced delayed recall of Rey figures at 5 min (His/His, 6.5 ± 0.1; His/Tyr, 5.5 ± 0.4; F = 5.7, d.f. = 1, P = 0.02) and 24 h after presentation (His/His, 6.2 ± 0.2; His/Tyr, 5.2 ± 0.5; F = 3.9, d.f. = 1, P = 0.05). In female subjects, none of these measures was significantly affected by genotype. Importantly, in the combined sample, the genotype did not affect performance in this difficult figural immediate recall test (His/His, 7.3 ± 0.1; His/Tyr, 7.1 ± 0.4; F = 0.1; d.f. = 1; P = 0.74). Moreover, the genotype did not affect performance in immediate recognition of 13 presented complex figures of Kimura (hits – false alarms: His/His, 6.8 ± 0.2; His/Tyr, 7.3 ± 0.5; F = 1.2; d.f. = 1; P = 0.28). Performance in these demanding immediate-memory tasks requires high levels of attention and motivation along with well-functioning working memory. Therefore, the identical performance between genotype groups in these tests indicates that the genotype-dependent differences in delayed verbal and figural episodic memory were not caused by genotype effects on confounding factors such as motivation, attention or working memory.

Taken together, our findings indicate that a functional genetic variation of the 5-HT2a receptor influences episodic memory in humans. The identification of genes accounting for the variability of distinct human memory processes provides new insights into the genetic basis of these polygenic cognitive abilities.

ACKNOWLEDGMENTS

This work was supported by grants from the Swiss National Science Foundation (3232-058420.99 to D.Q., and 32-068859, PP00B-68859/1 to A.P.), by the Hartmann-Müller-Stiftung (D.Q.) and by the National Center for Competence in Research (NCCR) "Neuronal Plasticity and Repair".

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Received 8 July; accepted 29 September 2003
Published online at http://www.nature.com/natureneuroscience/

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Olfactomotor activity during imagery mimics that during perception

Moustafa Bensafi[1], Jessica Porter[1], Sandra Pouliot[2], Joel Mainland[1], Bradley Johnson[1], Christina Zelano[1], Natasha Young[3], Elizabeth Bremner[1], Danny Aframian[1], Rehan Khan[1] & Noam Sobel[1,3]

Neural representations created in the absence of external sensory stimuli are referred to as imagery[1], and such representations may be augmented by reenactment of sensorimotor processes[2]. We measured nasal airflow in human subjects while they imagined sights, sounds and smells, and only during olfactory imagery did subjects spontaneously enact the motor component of olfaction—that is, they sniffed. Moreover, as in perception[3,4], imagery of pleasant odors involved larger sniffs than imagery of unpleasant odors, suggesting that the act of sniffing has a functional role in creating of olfactory percepts.

Imagery has been characterized in vision, audition and motor function[5], but olfactory imagery remains controversial[6]. In support of olfactory imagery, there is evidence of imagery-induced reductions (improvements) in odor threshold, imagery-enhanced olfactory recognition, similarity in perceptual grouping of real and imagined odors, and similarity in relative contributions of real and imagined odors to the perception of an odor mixture (for review, see ref. 7).

Whereas the existence of odor imagery may be supported by these reports, the process by which an olfactory image is created remains unknown. In vision, common processes underlie perception and imagery. For example, oculomotor responses during imagery are similar to those during perception[2]. As in visual perception, odor perception requires integration of sensory (smelling) and motor (sniffing) components. Sniffing alone (without odor) induces neural activity in the olfactory epithelium, olfactory bulb and olfactory cortices[8,9]. Furthermore, sniff attributes (flow rate duration and volume) are integral components of the olfactory percept[10]. To investigate whether sniffs are spontaneously generated during olfactory imagery, as are eye movements during visual imagery, we measured nasal airflow during the creation of auditory, visual and olfactory imagery in 30 subjects (see **Supplementary Note** online for further experimental details). Subjects were not made aware of the goal of the study or that airflow was being measured.

The first nasal inhalation after instruction to create an image was different across conditions ($F_{3,87}$ = 22.290, P < 0.0001): greater during olfactory mental imagery than during auditory mental imagery (t_{29} = 6.167, P < 0.0001), visual mental imagery (t_{29} = 5.472, P < 0.0001) and a baseline of ongoing nasal inhalation (t_{29} = 7.182, P < 0.0001; **Fig. 1a**). In other words, when imagining an odor, subjects sniffed.

[1]Helen Wills Neuroscience Institute and [3]Department of Psychology, University of California at Berkeley, 3210 Tolman Hall MC 1650, Berkeley, California 94720, USA. [2]Department of Psychology, Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, Quebec. Correspondence should be addressed to M.B. (bensafi@uclink.berkeley.edu).

Published online 19 October 2003; doi:10.1038/nn1145