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Research report

Evidence of *MAOA* genotype involvement in spatial ability in males

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HIGHLIGHTS

- Lacking evidence of monoamine-oxidase (MAO-A) involvement in human spatial memory.
- Participants performed a virtual Morris Water Maze task.
- High MAO-A activity males performed consistently better than low MAO-A activity males.
- Findings not due to pre-task differences or age.

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ABSTRACT

Although the monoamine oxidase-A (*MAOA*) gene has been linked to spatial learning and memory in animal models, convincing evidence in humans is lacking. Performance on an ecologically-valid, virtual computer-based equivalent of the Morris Water Maze task was compared between 28 healthy males with the low *MAOA* transcriptional activity and 41 healthy age- and IQ-matched males with the high *MAOA* transcriptional activity. The results revealed consistently better performance (reduced heading error, shorter path length, and reduced failed trials) for the high *MAOA* activity individuals relative to the low activity individuals. By comparison, groups did not differ on pre-task variables or strategic measures such as first-move latency. The results provide novel evidence of *MAOA* gene involvement in human spatial navigation using a virtual analogue of the Morris Water Maze task.

1. Introduction

Differences in the variable number of tandem repeats (VNTR) of the monoamine oxidase A gene (*MAOA*) have been linked to a variety of psychiatric disorders including anxiety [1,2], depression [3], or schizophrenia [4]. These disorders are typically associated with cognitive deficits, such as perturbations in spatial learning and memory in anxiety [5] and depression [6]. Therefore, variations in *MAOA* gene expression might also contribute to disease-related cognitive dysfunction such as executive attention [7], working memory [8] or decision-making [9]. This study examines this possibility, specifically in relation to spatial learning and memory.

Basic neuroscience studies support a role of *MAOA* in spatial abilities but have mostly measured *MAO* enzyme activity rather than transcriptional activity of genetic expression. In mice, the *MAOA* inhibitor moclobemide improved spatial performance and novel object exploration [10], whereas pinoline, a *MAOA* and serotonin-uptake inhibitor, reduced the number of arm entries and time spent in the open area of a plus maze [11]. Similarly, inhibition of *MAOA* increased locomotor activity in a water maze task but failed to facilitate spatial learning in adult rats [12]. While these data suggest that *MAOA* influences basic learning and memory processes, parallel evidence in humans remains limited.

To our knowledge, only one previous study in humans assessed the influence of platelet *MAO* on spatial abilities [13]. Their data [13] indicated an inspection time of a perceptual maze that was

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shorter in high-*MAO* activity males relative to low-*MAO* activity males, but similar in high-*MAO* activity males and low-*MAO* activity females. However, these earlier findings focused on the *MAO* enzymatic activity rather than *MAOA* genetic expression, and they were based on a paper-and-pencil maze, a small sample size, and a potential confound of gender. Improving on previous paper-and-pencil based tasks, ecologically-valid, computerized virtual mazes have become available to measure spatial navigation more precisely in humans. These virtual mazes have been shown to be sensitive to exposure to sex steroids [14], age-effects [15], and neurological damage [16].

The *MAOA* gene has a 30 base pair repeat in the promoter region (*MAOA*-LPR) that has been shown to affect transcriptional efficiency *in vitro*. Individuals with the long allele (3.5 repeats and 4 repeats) show greater transcriptional activity (high *MAO-A* gene activity) than individuals with the short allele (3 repeats) (low *MAOA* gene activity) [17]. Of note, the *MAOA* gene is located on the X-chromosome. Thus, women have two *MAOA* genes, whereas males have only one copy. While the comparison of high vs. low expressing gene is simple in males (single gene yielding only two genotypes, high vs. low expressing), it becomes more complex in females (two genes yielding 4 possible combinations of the low/high efficiency genes).

The present study evaluates the contribution of high and low monoamine oxidase gene expression by virtue of examining *MAOA*-LPR genotypes in human spatial learning and memory. As a first step, we limited the sample to males to exclude potential confounds of sex [18]. To circumvent issues with age-related cognitive declines in spatial abilities across the life-span [15] as well as age-dependent effects of *MAOA* on spatial performance [19], we specifically focused on young males. With regard to predictions, previous findings have been ambiguous. On the one hand, animal studies measuring enzyme activity suggest that subjects with low *MAOA* activity perform better on learning and memory tasks than subjects with high *MAOA* activity [10], supported by human genetic expression studies showing better performance in decision-making [9] and higher attainment of educational levels for low-activity individuals [20]. On the other hand, the reverse pattern, a better performance for individuals with the high-activity (long) allele relative to individuals with the low-activity (short) allele has been found in gene expression studies of executive attention [7] and working memory [8]. In addition, molecular work also shows higher transcriptional efficiency in carriers with the high-activity *MAOA* allele [17]. Thus, based on this mixed literature, we sought to compare long and short-allele carriers and expected significant differences between groups on spatial performance parameters on a virtual Morris Water Maze task [14,21].

2. Materials and methods

2.1. Experimental subjects

Sixty-nine healthy male adolescents, mostly of Caucasian ethnicity, participated in this experiment. Of these, 28 males (mean age = 19.39 ± SD 10.91; mean IQ: 114.18 ± SD 12.46) were hemizygous for the low (3) activity variant and 41 males (mean age = 16.37 ± SD 6.86; mean IQ: 116.05 ± SD 13.18) were hemizygous for the high (4) activity variant. Both groups were similar in age ($t(41.50) = 1.30$, $p = 0.20$) and IQ ($t(64) = -0.58$, $p = 0.56$), which was measured with the Wechsler abbreviated scale of intelligence [22]. Adult participants and the parents of minors provided written consent, and adolescents provided written assent to participate in protocols approved by the Institutional Review Board of the National Institute of Mental Health (NIMH). Inclusion criteria consisted of an absence of medical or psychiatric problems, as determined by physical examination and structured psychiatric interviews (Kiddie-Schedule-for-Affective-Disorders–Present-and-Lifetime-version [23]) administered by an experienced clinician (inter-rater reliability $k > 75$), absence of psychotropic medications or drug use and an IQ > 80.

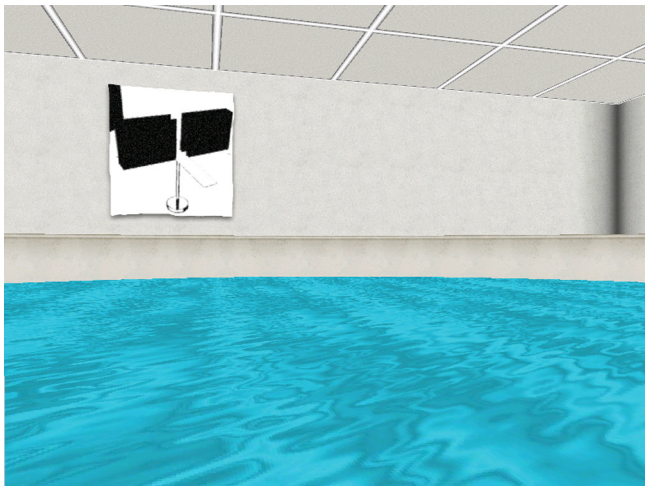

Fig. 1. Sample trial of virtual Morris Water Maze task.
Sample screenshot of a typical trial in which the person must navigate through the water maze from a first-person perspective with the distal cue (e.g., the painting) visible in the background.

2.2. Materials

A virtual version of the Morris Water Maze [21] was used. It consisted of the display of a square room containing a circular pool of water. Four equally-sized abstract rectangular paintings that were distinguishable by their shape, colour, and placement on the walls surrounding the pool, served as navigational cues to aid orientation. Each of these cues was placed on a different wall of the room and stretched from the ceiling to the pool wall (see Fig. 1). Participants navigated in the pool from a first-person perspective and moved around using the 'up', 'left' and 'right' arrow curser keys of the keyboard. Following previous authors' task-rules [16], to more closely mirror typical rodent behaviour, the 'back' arrow key was disabled and participants were told they could not back up. If participants wanted to turn around, they had to spin 180 deg around their left or right axis using the left or right arrow keys.

Participants completed the experiment on a laptop with a 17 inch monitor in a windowless room of the pediatric clinic of the NIH Clinical Center. The experiment was completed in one session without breaks and lasted about 15 min. Following previous investigators [24], the task consisted of 18 trials, including 2 initial practice trials and 16 experimental trials. On the first practice trial, participants had 30 s to explore the room and to learn to navigate comfortably in this environment. No platform was present during this first trial. The platform was introduced on the second practice trial. For this trial, participants were asked to simply "swim" towards the visible platform. Over the next 16 experimental trials, the platform was hidden but always located in the same position. However, the platform location was different from the second visible platform trial and participants had to 'hunt' for the platform on the first hidden trial. Participants were dropped in a pseudo-randomised order, which was fixed for all participants, across trials an equal number of times at four different locations on the side of the pool wall. For each trial, the task consisted of "swimming" directly to the hidden platform. Once participants successfully reached the platform, a neutral sound occurred. Participants remained on the platform for 2 s before the onset of the