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BRAIN RESEARCH

Research Report

Ventro-lateral prefrontal activity during working memory is modulated by MAO A genetic variation

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ABSTRACT

Several lines of evidence have highlighted the role of the serotonergic system in working memory (WM) processes. The X-linked Mono-Amine Oxidase A (MAO A) gene, coding for an enzyme especially involved in the serotonin (5-HT) catabolism, presents a well-characterized functional polymorphism consisting in a variable number of tandem repeats (VNTR) in the promoter region with high activity and low activity variants. The high activity allele carriers have been associated with higher enzyme expression, lower amine concentration and altered prefrontal cortex (PFC) function during motor inhibition, but a direct effect of MAO A genotype on WM-related brain activity has not been demonstrated. We have studied the relationship of this polymorphism to brain activity elicited by a spatial working memory task (*n*-back) using blood oxygenation level-dependent functional magnetic resonance imaging in 30 healthy male individuals matched for a series of demographic and genetic variables (COMT $Val^{108/158}$Met). We show that the high activity allele was significantly (p-level < 0,001) associated with increased activity of the right ventro-lateral PFC (VLPFC, BA 47) during the high load condition of the *n*-back task. Our data reveal pronounced genotype-related functional changes in specific prefrontal region (VLPFC) subserving spatial working memory. Moreover, given the well-known role of this area in inhibitory control, our finding also provides new evidence for the involvement of 5-HT in PFC-mediated WM function.

1. Introduction

The circuitry of the prefrontal cortex (PFC) has an established role in the working memory processes essential to human cognition (Goldman-Rakic, 1987). Several studies have shown that dopamine (DA) plays an important role in modulating the activity of this cortical area. However, there is compelling evidence that serotonin (5-HT) is also an important modulator of prefrontal brain function. The PFC is substantially innervated by serotonergic fibers from the dorsal raphe nucleus in both primates and

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Abbreviations: MAO A, Mono-Amine Oxidase A; 5-HT, serotonin; IFC, inferior frontal cortex; fMRI, functional magnetic resonance; VLPFC, ventro-lateral prefrontal cortex; WM, working memory

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Table 1 – Subject characteristics

	MAO A High activity	MAO A Low activity	p-value
N	16	14	
Age (y)	28.6±5.7	33.3±5.2	0.03
Educational level (y)	14.3±1.8	13.1±3.3	0.2
Depression	57.5±10.4	64±15.9	0.2
Anxiety	13.7±5	14.6±5.2	0.63
BIS-11	56 (range: 43–75)	60 (range: 41–75)	0.51
IQ	117.9±12.1	114.5±14.5	0.51
MCST (PE)	2.1±2.4	1.9±2.6	0.86
Accuracy 2-back (%)	78±16.3	77.5±16.7	0.93
Reaction time 2-back (ms)	352.4±146	425±186.6	0.24

Data are expressed as mean values (±SD), or median values (range) when appropriate. MCST (PE): Modified card sorting test, perseverative errors.

rodents (Smiley and Goldman-Rakic, 1996; Preece et al., 2004). Lesions of raphe nuclei induced by serotonergic neurotoxin significantly decreased working memory (WM) performance in rats performing a radial 8-arm-maze task (Hritcu et al., 2007). On the other hand, the results from human studies on the association between 5-HT and working memory performance have been controversial. Indeed, by using acute tryptophan depletion (ATD) to manipulate brain serotonergic function, some studies have showed impaired cognitive performance during reversal learning and continuous performance tasks (Park et al., 1994; Riedel et al., 1999), whereas some others have found little or no effect during the Wisconsin Card Sorting Test (Gallagher et al., 2003) and *n*-back task (Allen et al., 2006). Thus, the role of serotonergic system in working memory seems to be not yet clear.

A useful *in vivo* fMRI technique for investigating the relationship between the serotonergic system and WM processes is represented by imaging genetics (Meyer-Lindenberg and Weinberger, 2006). This is a strategy for mapping neural structure and activity as a function of genotype in living humans. Of the many allelic variants that have been identified in serotoninergic genes, those representing critical reduction in serotonin synthesis, reuptake and metabolism may lead to the most dramatic alterations in the serotonergic neurotransmission. In particular, catabolism of 5-HT is regulated by the activity of Mono-Amine Oxidase (MAO). MAO is a mitochondrial enzyme which degrades the neurotransmitters serotonin (and to a lesser extent) noradrenaline and dopamine (Shih and Chen, 1999). There are two distinct forms of the enzyme, A and B, with the isoform MAO A having much greater affinity for the 5-HT substrate (Shih and Chen, 1999). The MAO A coding gene (Xp11.4-Xp11.3) presents a well-characterized polymorphism, consisting of a variable number of tandem repeats (VNTR) in the promoter region, with different length variants that selectively influence the protein transcription and hence the enzymatic activity (Sabol et al., 1998; Denney et al., 1999). Enzyme expression is relatively high for carriers of 3.5 or 4 repeats (MAO A-High) and lower for carriers of 2, 3 or 5 repeats (MAO A-Low) (Sabol et al., 1998). Converging evidence suggests that this polymorphism strongly regulates the serotonergic function *in vitro* and *in vivo* (Sabol et al., 1998; Denney et al., 1999; Manuck et al., 2000) with the high activity allele showing the lowest serotonergic responsivity (Manuck et al., 2000). Functional imaging studies have recently began to show the genetic effect of this polymorphism on brain function. In particular, Fan et al. (2003) have found increased cingulate activation during conflict resolution in MAO A-High subjects, and Passamonti et al. (2006) have demonstrated that the response of inferior frontal cortex (IFC), elicited by a response inhibition paradigm (Go/NoGo), was increased in these individuals. Finally, a recent study reported the profound impact of the MAO A polymorphism on brain circuits involved in emotional memory having the highest density of serotonin receptors (Meyer-Lindenberg et al., 2006).

However, whether this functional polymorphism may modulate the neuronal activity of brain circuitry subserving working memory, and how, has not been demonstrated. To directly investigate the individual contribution of the MAO A VNTR polymorphism acting on this behavioral phenotype, we used a spatial "*n*-back" paradigm. We reasoned that if MAO A plays a role in modulating the serotonergic function, in particular in the IFC which presents a high expression of the MAO A protein (Varnas et al., 2004) and a dense serotonergic innervation (Anderson et al., 2002), then one might expect that the individuals carrying the allelic variant conferring a reduced serotonergic function would display an increased BOLD response of this area to compensate for reduced cortical efficiency (Hariri and Holmes, 2006). Moreover, because (1) MAO A polymorphism has been

Table 2 – Brain response for the main effect of task (2-back vs. 0-back) in the normal cohort

Within group analysis	Brodmann area (BA)	Talairach coordinates x	y	z	Z-score	Cluster-size
Right parietal cortex						
Inferior parietal lobule	19/40	50	−40	46	6.93	8340
Superior parietal lobule	7	32	−56	47	7.3	8340
Left parietal cortex						
Inferior parietal lobule	40	−44	−50	50	4.50	396
Superior parietal lobule	7	−32	−56	42	5.55	396
Medial frontal cortex						
Left premotor cortex	6	−40	4	37	6.38	1787
Pre-SMA	8	−2	22	47	6.89	806
Right prefrontal cortex						
Dorso-lateral	9/46	40	44	24	6.64	4619
Ventro-lateral	45/47	38	19	−6	6.49	4619
Left prefrontal cortex						
Dorso-lateral	9/46	−40	49	14	6.08	1787
Ventro-lateral	45/47	−32	23	5	6.13	977
Left thalamus		−10	−7	11	5.31	413
Right thalamus		8	15	14	5.24	587
Left caudate nucleus		−16	−7	22	5.01	413
Right caudate nucleus		8	−11	23	5.00	587
Left cerebellum		−10	−77	−21	5.13	662
Right cerebellum		31	−64	−17	5.01	662

N=30. One sample t-test, $p<0.001$, corrected for multiple comparisons.