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Brief report

The MAO-A genotype does not modulate resting brain metabolism in adults

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Abstract

Variation in the monoamine-oxidase-A (MAO-A) gene has been associated with volumetric changes in corticolimbic regions with differences in their response to relevant emotional tasks. Here we show no changes in baseline regional brain metabolism as a function of genotype indicating that, unchallenged, corticolimbic activity is not modulated by the MAO-A genotype.
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1. Introduction

Monoamine oxidase A (MAO-A) degrades neurotransmitters, including serotonin, dopamine and norepinephrine implicated in regulating mood and behavior (Shih and Thompson, 1999). A functional polymorphism in the MAO-A gene promoter is described as 4-tandem-repeats (high MAO-A activity) in 60% and 3-repeats (low MAO-A activity) in 40% in healthy men (Sabol et al., 1998). Studies in humans (Foley et al., 2004) and primates (Newman et al., 2005) support a link between the low MAO-A genotype and susceptibility to antisocial behavior in the face of childhood maltreatment. Functional magnetic resonance imaging (fMRI) studies found that healthy subjects with the low MAO-A genotype have mostly reduced volume (Meyer-Lindenberg et al., 2006) and different patterns of cortical activity in the performance of cognitive and emotional tasks compared with the high MAO-A genotype (Fan et al., 2003; Passamonti et al., 2006; Meyer-Lindenberg et al., 2006).

It is not known, however, whether brain function assessed in a resting condition, as opposed to a cognitive or emotional task, would differ as a function of the MAO-A genotype. As compared with fMRI, glucose utilization measured by PET is a quantifiable and absolute measure of brain activity. Using the aggregation of brain activity over time without a specific challenge, yet with subjects in an alert state, may provide an informative *gestalt* of baseline

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neuronal activity. We hypothesized that brain function without any task, therefore without a specific challenge to expose susceptibility, would not show genotype-modulated differences in brain metabolism.

2. Method

Thirty-eight male subjects (32±6 years of age) participated in a positron emission tomograph (PET) study after a thorough physical examination and interview by a neurologist to verify healthy status. All 38 control subjects were fasting 4 h before this PET study. Non-smoking status was ascertained by self-report and verified by breath CO test. Two PET scans were obtained 2 h apart at rest: a [^{11}C]clorgyline [reported elsewhere (Fowler et al., 2007)] followed by an ^{18}FDG scan to measure glucose metabolism, both carried out with the subjects at rest.

All subjects provided cheek swab samples containing their DNA, which was analyzed for MAO-A (Freeman et al., 2003). Polymerase chain reactions (PCRs) were performed as described previously (Sabol et al., 1998). The PCR products were analyzed on an Applied Biosystems 3100 Genetic analyzer resulting in 12 subjects (32%) having the 3-repeat allele (low) and 26 (68%) having the 4-repeat allele (high), distributions that parallel those reported in previous studies (Meyer-Lindenberg et al., 2006). Note that we did not have subjects with 3.5 or 5 repeat alleles in this sample, possibly due to the relative rarity of these alleles in the population (less than 2%). There were no significant differences between the two genotype groups on age, education, right hand dominance (Oldfield, 1971), socioeconomic status (Hollingshead, 1958), verbal (Wilkinson, 1993) and non-verbal (Wechsler, 1999) measures of intelligence, and self-reported depression (Beck et al., 1996) (all $P>0.62$). Subjects were fully informed and provided written consent in accordance with the local Institutional Review Board.

The ^{18}FDG scans were acquired on a whole body PET scanner (Siemens HR+4.5×4.5×4.8 mm at center of field-of-view) in 3D mode providing 63 contiguous planes of 2.4 mm each. To stabilize the head, an individually molded head-holder was made for each subject. Subjects were kept supine with their eyes open in a quiet room with a nurse monitoring to prevent sleep and maintain awake state. Catheters were placed in the antecubital vein for radiotracer injection and the radial artery for blood sampling. A transmission scan was obtained with a ^{68}Ge rotating rod source before the emission scan to correct for attenuation before the radiotracer injection. Then, ^{18}FDG (Hamacher et al., 1986) (3–5 mCi) was injected. Serial blood samples were taken from time of ^{18}FDG injection through 55 min. Emission data were attenuation-corrected and reconstructed using filtered back projection and metabolic images were computed (Reivich et al., 1985).

Data were analyzed using Statistical Parametric Mapping (SPM) (Friston et al., 1995) on the "absolute" and the "relative" (images normalized to the mean metabolic activity of all voxels within the brain) metabolic images. The relative scaling corrects for these individual differences by accounting for differences in global metabolism. For this purpose the metabolic measures were spatially normalized using a $2\times2\times2$ mm^3 voxel size and the template provided in the SPM 99 package and subsequently smoothed with a 16-mm isotropic Gaussian kernel. Two separate independent-samples *t*-tests were performed to compare the absolute and the relative images obtained from the participants during rest.

Manual regions of interest (ROIs) were also drawn on the metabolic images of each subject. For ROI placement we re-sliced the metabolic images along the anterior commissure-posterior commisure (AC-PC) line and summed the 63 planes in groups of two, obtaining 23 planes of 4.76 mm thickness with 11 planes above and 11 planes below the thalamus. We applied a Talairach and Tournoux (1988) template while manually adjusting the position of the ROI for each individual. Values were computed using the weighted average from the different planes for the regions in Fig. 1. Each of these ROIs was identified in at least two contiguous slices. To obtain a global metabolic value for each individual, we chose 10–12 of these planes (depending on the size of the

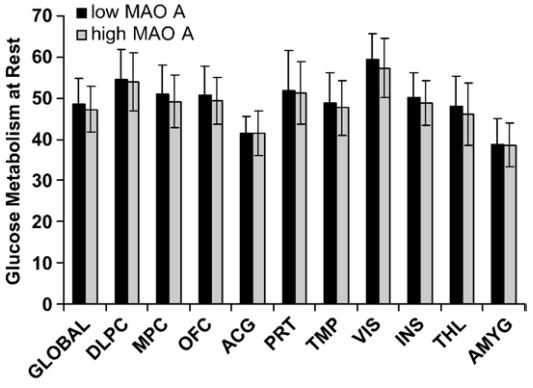

Fig. 1. Absolute glucose metabolism at rest in the low and high MAO-A genotype groups. From manually drawn bilateral (averaged) ROIs in dorsolateral prefrontal cortex (DLPC), medial prefrontal cortex (MPC), lateral orbitofrontal cortex (OFC), anterior cingulate gyrus (ACG), parietal cortex (PRT), medial and lateral temporal cortices (TMP), the visual cortex (VIS), insula (INS), thalamus (THL) and amygdala (AMYG). Error bar represents standard deviation.

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individual brain), typically choosing 6–7 planes above and 4–5 planes below the thalamus using a program that thresholded at 20% of the maximum metabolic rate for the plane (Volkow et al., 2006).

Whole-brain SPM significance was set at $P<0.05$, cluster-level corrected, though uncorrected thresholds were also inspected. The ROIs from manual drawings are reported at the threshold level of $P < 0.05$, Bonferroni corrected for regions implicated in the MAO-A genotype (Buckholtz et al., 2008).

3. Results

On the basis of whole brain analyses in SPM, there were no significant differences in absolute or relative baseline metabolism between the genotyped groups. When the significance threshold was reduced to $P < 0.05$, uncorrected, there were still no differences in absolute or relative metabolism. The ROI results confirmed the nonsignificant SPM findings (all $P>0.30$) (Fig. 1).

4. Discussion

Baseline metabolism, a marker of resting brain function (Volkow et al., 2006), did not differ as a function of the MAO-A genotype. Post hoc analysis revealed that the sample size in this study would yield a power of 80% for the *t*-test to detect differences at effect size 1 ($P<0.05$, two-tailed). In our study the pooled S.D. was about 20% of the population mean. This indicates that the effect of MAO-A genotype on brain metabolism at rest is smaller than the variability in brain metabolism at rest in adult subjects. Failure to see a difference could reflect the need to challenge subjects with a relevant task to detect the differences in activation patterns as a function of genotype. Given volumetric differences in amygdala and cingulate that were observed as a function of genotype (Meyer-Lindenberg et al., 2006), one would expect differences in metabolism unless the lack of a challenge created a ceiling effect in these healthy subjects.

This finding mirrors our negative results in the same sample with [^{11}C]clorgyline, a radiotracer with specificity for brain MAO-A (Fowler et al., 2007). It appears that the MAO-A genotype has a modulatory effect on neuronal maturation in utero, and is relevant in childhood only through sensitivity to environmental insult (Caspi et al., 2002) and in adulthood through reactivity to emotional stimuli in fMRI studies (Meyer-Lindenberg et al., 2006). However, fMRI experiments cannot measure brain function at absolute baseline, making it difficult to distinguish differences due to the task challenge from those pertaining to general brain function at baseline (Canli et al., 2005). Although Independent Component Analysis (ICA) can detect baseline fluctuations and map regions that have similar time-varying responses, ICA does not provide absolute measures in fMRI. Since we measure a substantial period of time when the brain is not harnessed to task demands, we call this "absolute baseline". Here we show that at resting baseline, the MAO-A genotype does not impart a significant effect on glucose metabolism in brain.

This finding corroborates our hypothesis that in the context of externalizing behavior phenotypes (such as antisocial behavior), significant associations between genotype and behavior emerge primarily in response to a challenge that serves to perturb the individual beyond his or her baseline state.

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