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The correlation between striatal dopamine D_2/D_3 receptor availability and verbal intelligence quotient in healthy volunteers

JIN FU GUO[1], YEN KUANG YANG[1]*, NAN TSING CHIU[2], TZUNG LIEH YEH[1], PO SEE CHEN[1], I. HUI LEE[1] AND CHING LIN CHU[1]

Departments of [1] Psychiatry and [2] Nuclear Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

ABSTRACT

Background. Although a correlation between the central dopaminergic system and intelligence may exist, the results from imaging studies remain inconclusive. The aim of this study was to explore the relationship between striatal dopamine D_2/D_3 receptor availability and verbal intelligence quotient (VIQ) using single photon emission computed tomography (SPECT).

Method. Striatal D_2/D_3 receptor availability of 64 healthy subjects was determined with the [^{123}I]iodobenzamide ([^{123}I]IBZM) ligand. Intelligence quotients (IQs) of the subjects were measured by the Wechsler Adult Intelligence Scale – Revised (WAIS-R).

Results. In addition to age, left striatal D_2/D_3 receptor availability correlated positively with VIQ. In females, left striatal D_2/D_3 receptor availability was the only variable that correlated significantly with the similarities subtest of VIQ.

Conclusions. There is a relationship between left striatal D_2/D_3 receptor availability and verbal intelligence, which varies, predominantly in males.

INTRODUCTION

Previc (1999) proposed that human intelligence may be related to an expansion of the central dopaminergic system. From the viewpoint of evolution, this theory has two major tenets associated with it. The first is that dopamine is essential to motor activities and physical endurance, which were necessary to the survival of our ancestors. The second is that dopamine is an important neurotransmitter involved in abstract intellectual behaviors and language skills. Both skills were important for acquiring the social resources necessary for survival.

Dopamine is postulated to be one of the important neurotransmitters that regulate several domains of cognitive functions (Previc, 1999). Unrelated to physical or mental symptoms, reduced dopaminergic neurotransmission in elderly people and patients with Parkinson's disease is characterized by reduced speed of cognitive processing and visuospatial performance (Cooper & Howell, 1993; Barili *et al.* 1998). Fine motor control and attention scores are also correlated with striatal D_2/D_3 availability in patients with schizophrenia (Yang *et al.* 2003; 2004). The dopamine D_2 receptor (DRD2) gene has also been reported to be associated with neurophysiological, neuropsychological and personality characteristics (Noble, 2003). Berman and Noble (1995) studied family members of alcoholics and reported that children with the A_1 allele of D_2 receptors have poor visuospatial abilities. However, their results do not agree with those of other studies (Petrill *et al.* 1997; Moises *et al.* 2001).

* Address for correspondence: Dr Yen Kuang Yang, Department of Psychiatry, College of Medicine, National Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan.
(Email: ykyang@mail.ncku.edu.tw)

Jonsson *et al.* (1999) reported a significant association between the presence of a putative functional DRD2 promoter allele and high striatal dopamine receptor density. They suggested that the polymorphism of the DRD2 gene may result in different striatal dopamine receptor densities. In addition, Thompson *et al.* (1997) discovered a correlation between the A_1 allele of the DRD2 gene and reduced dopamine D_2 receptor binding ability in the human striatum.

Several magnetic resonance imaging (MRI) studies have found a correlation between the brain sizes of healthy subjects and their intelligence quotients (IQs), and a small positive correlation between the volume of the basal ganglia and IQ has been reported (Andreasen *et al.* 1993; Reiss *et al.* 1996). Some studies have indicated that basal ganglia have an effect on cognitive functions such as action-orientated and sensory-motor cognition (Filipek *et al.* 1997; Giedd *et al.* 1999; Sears *et al.* 1999; Porrino *et al.* 2004). In addition, Levitt *et al.* (2002) showed that the volume of the head of the caudate nucleus correlates positively with the working memory of subjects with schizotypal disorder. Other studies have attempted to find direct evidence of the relationship between striatal dopamine D_2 bindings and intelligence, although their results are inconsistent and the samples and methods differ (Lawrence *et al.* 1998; Volkow *et al.* 1998).

Although lateralization has been shown to be involved in various cognitive tasks (Beauchamp *et al.* 2002; Yang *et al.* 2002; Liu *et al.* 2004), the relationship between central dopaminageric lateralization and human intelligence has not been elucidated before. Because of the high degree of heterogeneity in human intelligence, subcategorizing intelligence is necessary when analyzing the neuromodulator influence of dopamine on intelligence. Mozley *et al.* (2001) demonstrated that striatal dopamine transporter availability is correlated with verbal learning ability. Chen *et al.* (2005) also found that verbal memory scores are significantly correlated with striatal D_2/D_3 receptor binding. It seems that central dopamine function may correlate with various cognitive tasks, particularly those involving verbal abilities.

The aim of this study was to explore whether a relationship exists between striatal D_2/D_3 receptor availability and IQ, particularly VIQ.

METHOD

Subjects

Before any procedure was performed, informed consent was obtained from the volunteers. The Ethical Committee for Human Research at the National Cheng Kung University Medical Center had approved the study protocols. We recruited 64 healthy volunteers; 35 males and 29 females. These volunteers were interviewed by a senior psychiatrist using the Chinese version of the Mini-International Neuropsychiatric Interview (Sheehan *et al.* 1998) to exclude individuals with mental illness. None of the volunteers had a history of significant physical illness. The average age was 36·11 years (S.D. = 11·95) in males and 38·59 years (S.D. = 11·32) in females. All of the subjects underwent the Wechsler Adult Intelligence Scale – Revised (WAIS-R) test (Wechsler, 1986), which includes digit symbol, block design, object assembly, digit span, similarity, and arithmetic tests. The former three measure non-verbal performance IQ (PIQ) while the latter three measure verbal IQ (VIQ).

Single photon emission computed tomography (SPECT) image acquisition and processing

Before SPECT examination with [^{123}I]iodobenzamide ([^{123}I]IBZM), the thyroid gland was protected with 9 ml of Lugol's solution. For brain SPECT imaging, each subject was intravenously administered 185 MBq (5 mCi) of [^{123}I]IBZM in a quiet environment approximately 10 min after setting the intravenous lines. Imaging was initiated 120 min post-injection according to *in vivo* kinetic data, which showed that specific striatal binding of IBZM was at a high steady-state level at this time (Hierholzer *et al.* 1992). We used a triple-headed rotating gamma camera (Multispect 3; Siemens, Hoffman Estates, IL, USA) with ultra-high-resolution fan-beam collimators, which yielded an image resolution of approximately 8·5 mm full-width at half-maximum (FWHM). The SPECT images were acquired over a 360° rotation, 120 steps, 50 s per step, in a $128 \times 128 \times 16$ matrix. The images were then reconstructed using Butterworth and ramp filters (cut-off frequency 0·3 Nyquist, power factor 7) with attenuation correction by Chang's method (Chang, 1978). The reconstructed transverse images were realigned parallel to the canthomeatal line. The slice thickness of each transverse image was 2·89 mm.

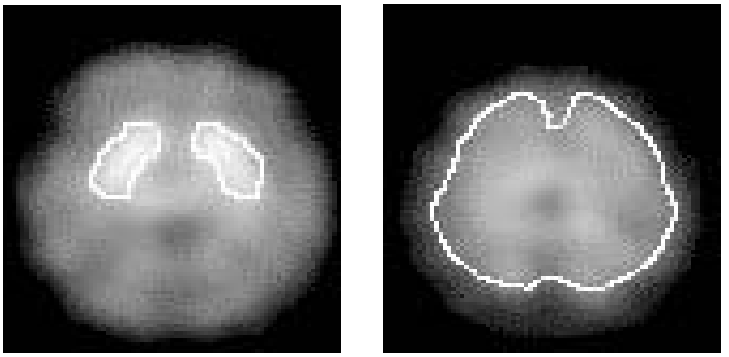

FIG. 1. The regions of interests (ROIs) of striatum (left) and supertentorium (right).

The WAIS-R test and brain SPECT imaging were performed on the participants starting at 10:00 hours. All participants completed the WAIS-R test and underwent brain SPECT imaging within 2 consecutive days.

Image analysis

To assess the radiotracer uptake in the brain, we used SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK) (Friston *et al.* 1995) to create a mean image of all the SPECT images. We then normalized all the participants' images to this mean image by a 12-parameter affine (linear) transformation. For this procedure, the anterior commissure had to be defined. MRI images (GE Signa CV-I, 1.5 T, USA) of the healthy volunteers were used as a rough guide (non-registered) to visually determine the anterior commissure. An experienced nuclear-medicine physician who was blind to the participants' clinical data performed the process. He also selected 10 transverse slices from the mean image to define the regions of interests (ROIs) of the striatum and supertentorium. The supertentorium was delineated 12 mm above the uppermost part of the striatum (Fig. 1).

The standard ROIs were superimposed onto the normalized images without changing the size, shape or location. Then the striatal D_2/D_3 densities of ROIs were measured. Striatal D_2/D_3 densities were calculated with reference to the supertentorium, which is defined as $(Str-ST)/ST$, where Str and ST are the mean counts per pixel in the striatum and supertentorium respectively. Dividing by the supertentorium counts per pixel reduces between-subjects differences in D_2/D_3 receptor binding abilities. We used the supertentorium as a reference region instead of the occipital cortex or cerebellum because (1) the density of D_2/D_3 receptors is negligible in this region compared to the striatum (Lidow *et al.* 1989); (2) [^{123}I]IBZM activity in the neocortex is equal to the non-specific activity in the striatum (Seibyl *et al.* 1992); and (3) the reproducibility of non-specific binding may be better when compared with the relatively small regions of the cerebellum and occipital cortex (Mozley *et al.* 2000). Densities for left and right hemispheres were calculated separately. This ratio provides an objective estimate of D_2/D_3 receptor availability (Brucke *et al.* 1991; Hierholzer *et al.* 1992; Toyama *et al.* 1993).

Statistical analysis

Partial correlation and multiple linear regression were used. In addition, Hochberg's sharpened Bonferroni correction was applied for multiple comparisons. Age and sex were also included in the models as explanatory variables.

RESULTS

The correlation matrix among subtests of IQ and D_2/D_3 availability and other variables are shown in Table 1. Age correlated most significantly with VIQ and full-scale IQ (FIQ). The means of right and left striatal D_2/D_3 availability ratios, $(Str-ST)/ST$, were 0·74 (S.D. = 0·12) and 0·74 (S.D. = 0·13) respectively. The

Table 1. *Correlation matrix of IQ and dopamine D_2/D_3 receptor availability ($n=64$)*

	Digit span	Similarities	Arithmetic	Digit symbol	Block design	Object assembly	PIQ	VIQ	FIQ
Left striatal D_2/D_3 availability									
r[a]	0·14	0·28*	0·09	0·09	0·16	−0·15	0·04	0·22	0·15
p	0·26	0·02	0·48	0·49	0·20	0·24	0·78	0·08	0·25
Right striatal D_2/D_3 availability									
r	0·15	0·21	0·17	0·09	0·06	−0·07	0·04	0·22	0·14
p	0·23	0·10	0·18	0·46	0·66	0·60	0·79	0·08	0·29
Age (yr)									
r	−0·59***	−0·19	−0·27*	−0·32*	−0·27	0·02	0·02	−0·45***	−0·309*
p	0·001	0·14	0·03	0·01	0·03	0·86	0·91	0·001	0·01
Sex (male = 1, female = 0)									
r	0·14	0·07	0·08	−0·14	0·07	0·11	0·01	0·18	0·10
p	0·26	0·59	0·51	0·27	0·58	0·38	0·96	0·16	0·41

PIQ, performance IQ; VIQ, verbal IQ; FIQ, full-scale IQ.
[a] The correlation with dopamine striatal D_2/D_3 receptor availability in the striatum based on Pearson's product-moment.
* $p<0·05$, *** $p<0·001$ (two-tailed).

right-side ratios ranged from 0·49 to 1·03 while left-side ratios ranged from 0·38 to 0·95. The regression results indicated that the increase in the left striatal D_2/D_3 receptor availability, but not the right D_2/D_3 availability, was associated with higher VIQ after controlling for age and sex. However, the association between left/right striatal D_2/D_3 receptor availability and PIQ/FIQ was not significant (Table 2). The scatter plot of left striatal D_2/D_3 receptor availability *versus* VIQ is shown in Fig. 2.

Males and females were analyzed separately. The results of partial correlation after controlling for age showed that there was no significant correlation between striatal D_2/D_3 availability and scores of PIQ, VIQ or FIQ in either females or males. As for the subtests of IQ, the results of partial correlation with Hochberg's sharpened Bonferroni correction showed that the left striatal D_2/D_3 receptor availability was significantly correlated with the similarity subtest score of VIQ in females ($r=0·41$, $p=0·03$). There was no similar association in males.

DISCUSSION

Basal ganglia are involved in frontal subcortical circuits (Mega *et al.* 1997). Bartres-Faz *et al.* (2002) used MRI to demonstrate that reduced left caudate nucleus volume, part of the striatum, is associated with poor scores in the Mini-mental State Examination. The caudate nucleus and putamen have also been reported to be related to verbal functions (Belton *et al.* 2003). IQ scores have been correlated not only with the volume of the whole brain but also with that of the basal ganglia (Andreasen *et al.* 1993; Reiss *et al.* 1996; Frangou *et al.* 2004).

Dopamine influences are mainly exerted on the frontal lobe and basal ganglia. Damage to the basal ganglia may lead to dopamine transmission deficits. Furthermore, the largest and most significant projection of the caudate is directed towards the frontal lobes, which modulate major cognitive functions. As basal ganglia are closely linked to the cortical areas, alterations in the basal ganglia may ultimately result in cognitive deficits (Previc, 1999; Nieoullon, 2002). In addition, the striatum also has a direct connection to the nucleus reticularis of the thalamus, which modulates thalamocortical transmission. This may suggest that the striatum operates in conjunction with both the frontal cortex and the thalamus. It is possible that the above-mentioned tracts may be highly correlated with IQ scores.

Neuropsychological studies of subjects with brain lesions and advanced brain imaging techniques have shed light on fundamental aspects of cognitive lateralization in the left hemisphere, particularly in language (Crespo-Facorro *et al.* 1999; Pihlajamaki *et al.* 2000; Wharton *et al.* 2000). However, little is known about which substrates are involved in lateralization. It has been postulated that a dopaminergic expansion during early hominid evolution might have enabled the mastery of hunting skills (Previc,

Table 2. *Multiple linear regression analysis of IQ* ($n=64$)

Independent variables	PIQ β (S.E.)	VIQ β (S.E.)	FIQ β (S.E.)
Age (yr)	0·02 (0·16)	−0·46 (0·16)**	−0·31 (0·15)*
Sex (male = 1, female = 0)	−0·01 (3·85)	0·09 (3·19)	0·05 (3·66)
Left striatal D_2/D_3 availability[a]	0·02 (31·19)	0·24 (15·42)*	0·23 (29·84)
Right striatal D_2/D_3 availability[a]	0·03 (29·93)	−0·08 (30·78)	−0·09 (28·64)
R^2	$R^2=0·002$ ($F=0·03$; df = 4, 59)	$R^2=0·26$ ($F=10·85$; df = 2, 61)	$R^2=0·10$ ($F=6·55$; df = 1, 62)

Str, striatum; PIQ, performance IQ; VIQ, verbal IQ; FIQ, full-scale IQ.
[a] Striatal D_2/D_3 receptor availability, (Str − ST)/ST, was calculated using supratentorium (ST) as reference.
* $p<0·05$, ** $p<0·001$ (two-tailed).

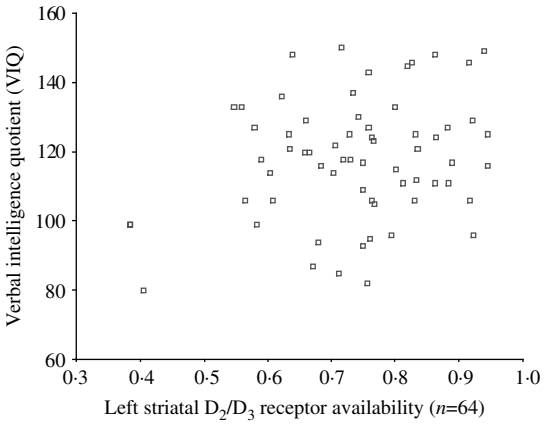

FIG. 2. Scatter plot of left striatal D_2/D_3 receptor availability *versus* verbal intelligence quotient (VIQ).

1999). In turn, changes in diet, physical activities and brain volume may have an effect on central dopamine. However, the precise mechanism is not known.

DNA methylation plays an important role in the epigenetic mechanism of the brain. Popendikyte *et al.* (1999) claimed that the degree of DNA methylation is significantly different between the right and left striatum. The degree of striatal methylation also varies with age. In addition, the DRD2 gene plays an important role in DNA methylation. This may explain the right–left asymmetry of striatal D_2/D_3 receptor availability (Larisch *et al.* 1998; Lee *et al.* 2005) and the correlation between left striatal D_2/D_3 receptor availability and VIQ in healthy controls.

Our results suggest that VIQ was correlated with left striatal D_2/D_3 receptor availability. This finding is in accordance with some genetics-based studies (Berman & Noble, 1995; Tsai *et al.* 2002) but not all (Moises *et al.* 2001). Volkow *et al.* (1998) did not find a positive correlation between striatal D_2 receptor availability and IQ in their imaging-based study. The inconsistency may be due to several differences between the study by Volkow *et al.* and the current study. First, the left and right striatum were treated independently in our study while Volkow *et al.* considered the striatum as a whole. In our study, the correlation between striatal D_2/D_3 availability and IQ became insignificant when the effects of laterality and sex were neglected. Second, Volkow *et al.* used an FIQ score, which is dependent on both VIQ and PIQ. Because of the difficulty in interpreting the findings related to FIQ scores, we examined the relationship between striatal D_2/D_3 receptor availability and each IQ score separately, rather than considering the sum of different IQs as in Volkow *et al.* (1998). These differences may account for some of the inconsistencies between the two sets of results.

The present study replicated the results of earlier investigations that reported that younger healthy participants performed significantly better than their older counterparts on the function of memory or attention (Lezak, 1995). Our results demonstrated that higher specific uptake values in females, reflecting higher dopaminergic tone, correlated with a better similarity score in VIQ. Similar findings have been reported by Mozley *et al.* (2001), who

demonstrated that striatal dopamine availability correlated with learning performance in females but not in males. The reasons for sex differences in the neuromodulatory influences of dopamine on behavior/cognitive function are still unclear. As estrogen regulates dopamine transmission, sex hormones probably contribute to the sex differences (Halbreich, 1997; Lindamer *et al.* 1997; Nordstrom *et al.* 1998). We do not know why only the similarity subtest score correlated with striatal D_2/D_3 receptor availability.

Our study has several limitations. First, it is an association study. As it does not depend on experimental manipulations of dopaminergic tone to produce changes in intelligence, the causal relationship between striatal dopaminergic activities and VIQ cannot be confirmed. Second, the changes in central dopamine might not be fully accounted for by the single-site model used in this study (Laruelle, 2000). Third, the correlation between D_2/D_3 receptor availability and VIQ may not be directly attributable to dopaminergic density, but may be due to the synaptic dopamine level. Fourth, different phases of the menstrual cycle and different estrogen levels may influence the dopamine transmission, particularly during the late luteal phase and at the onset of menses (Dluzen & Horstink, 2003). Thus, the effect of the menstrual cycle should be considered in future. Finally, there were two participants with lower educational levels than most of the other participants and who demonstrated lower D_2/D_3 receptor ratios. If they were treated as outliers, the above-mentioned significant association would disappear. However, it is not appropriate to remove the two data points because they fit the inclusion criteria. Most of the volunteers were recruited from our university campus and had a higher IQ and were more educated (FIQ: 118, S.D. = 13·6; 71% of their educational levels are university degrees or above). Therefore, more heterogeneous subjects should be included in future to confirm the relationship between left striatal D_2/D_3 receptor availability and the similarity score.

Because of the high degree of heterogeneity in human intelligence, the weak association we found between striatal D_2/D_3 receptor availability and VIQ only offers a potential theoretical framework for future studies on human intelligence.

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DECLARATION OF INTEREST

None.

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