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Alteration of monoamine receptor activity and glucose metabolism in paediatric patients with anticonvulsant-induced cognitive impairment

Yuankai Zhu,[1-4†] Jianhua Feng,[5†] Jianfeng Ji,[1-4†] Haifeng Hou,[1-4] Lin Chen,[1-4] Shuang Wu,[1-4] Qing Liu,[1-4] Qiong Yao,[1-4] Peizhen Du,[1-4] Kai Zhang,[1-4] Qing Chen,[1-4] Zexin Chen,[6] Hong Zhang[1-4] and Mei Tian[1-4*]

[1]Department of Nuclear Medicine, The Second Hospital of Zhejiang University School of Medicine, Hangzhou, China; [2]Zhejiang University Medical PET Centre, Zhejiang University, Hangzhou, China; [3]Institute of Nuclear Medicine and Molecular Imaging, Zhejiang University, Hangzhou, China; [4]Key Laboratory of Medical Molecular Imaging of Zhejiang Province, Hangzhou, China; [5]Department of Paediatrics, The Second Hospital of Zhejiang University School of Medicine, Hangzhou, China; [6]Department of Clinical Epidemiology & Biostatistics, The Second Hospital of Zhejiang University School of Medicine, Hangzhou, China

†These authors contributed equally to this paper.

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*Correspondence:

Prof. Mei Tian, Department of Nuclear Medicine, The Second Hospital of Zhejiang University, 88 Jiefang Road, Hangzhou, Zhejiang 310009, China. E-mail: meitian@zju.edu.cn

ABSTRACT

A landmark study from the Institute of Medicine (IOM) reported that the assessment of cognitive difficulties in children with epilepsy is timely and imperative. Anticonvulsant-induced cognitive impairment could influence the quality of life more than seizure itself in patients. Although monoaminergic system is involved in the regulation of cognitive process, its role in anticonvulsant-induced cognitive impairment remains unclear.

Methods: To explore *in vivo* monoamine receptor binding activity in patients with anticonvulsant-induced cognitive impairment, each patient had PET imaging with both monoamine receptor binding agent, ^{11}C-N-methylspiperone (^{11}C-NMSP), and glucose metabolic agent, ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Tests of Intelligence quotient (IQ), including verbal intelligence quotient (VIQ), performance IQ (PIQ) and full-scale IQ (FSIQ) were performed in each patient.

Results: Compared to the patients with mono-therapy, patients with poly-therapy had significantly lower VIQ, PIQ and FSIQ ($P < 0.01$ in each comparison), as well as significantly lower monoamine receptor activities detected in the caudate nucleus, prefrontal cortex, dorsal anterior cingulate cortex and amygdale ($P < 0.05$ in each comparison). However, regarding to the glucose metabolism, there was no significant difference was found in patients with mono-therapy or poly-therapy ($P > 0.05$).

Conclusion: Monoamine receptor-PET imaging could be a promising *in vivo* imaging biomarker for mapping anticonvulsant-induced cognitive impairment.

Key Words: epilepsy; cognition; anticonvulsant; monoamine receptor; positron emission tomography (PET)

INTRODUCTION

A landmark study from the Institute of Medicine (IOM) reports that the chance of developing epilepsy at some point in our lives is 1 in 26, and recommends that the assessment of cognitive difficulties in children with epilepsy is timely and imperative (*1*). Cognitive impairment is the most common side effect of anticonvulsant, and the risk may accumulate when anticonvulsants are combined (*2*). Particularly, the developing brains of paediatric patients appear to be particularly sensitive to the cognitive adverse effects of anticonvulsants due to the age-related pharmacokinetic and pharmacodynamic features (*3*).

Positron emission tomography (PET) is ideally suited for monitoring cell/molecular events early in the course of a disease, as well as during pharmacological or radiation therapy (*4*). Among PET radioligands for mapping postsynaptic monoamine receptors, carbon-11-labeled raclopride (^{11}C-raclopride) is the most often used as a standard D_2 dopamine receptor (D_2DR) ligand (*5*). However, since the binding of ^{11}C-raclopride to the D_2DR in the striatum is competitive with that of endogenous dopamine and reversible in the time frame of a PET scan, it could not reflect the actual changes of postsynaptic receptor level. In contrast, ^{11}C-N-methylspiperone (^{11}C-NMSP), as a D_2 and 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptors antagonists, not competitive with that of endogenous dopamine (*5, 6*) and serotonin (*7*), its binding can directly reflect postsynaptic monoamine receptor level more accurately compared with ^{11}C-raclopride. Although monoaminergic system is involved in the regulation of cognitive process, its role in anticonvulsant-induced cognitive impairment remains unclear (*8, 9*). Therefore, we performed ^{11}C-NMSP PET studies to examine the alteration of monoamine receptor activity in paediatric patients with anticonvulsant-induced cognitive impairment.

MATERIALS AND METHODS

Subjects

Twenty-five patients (13 males, mean age of 13.7 ± 2.0 years) diagnosed with epilepsy (*10*) were enrolled in this study (Table 1). Sixteen right-handed healthy controls participants (9 males, mean age of 21.6 ± 1.3 years) with no history of neuropsychiatric disorders or receiving psychoactive drugs were included. The Institutional Review Board approved this study (ChiCTR-DDD-15007423), and the written

informed consent was obtained from each participant.

The patient inclusion criteria were as follows: (i) clinical and electroencephalogram (EEG) findings indicative of focal seizure, (ii) age 10–18 years, (iii) receiving at least one anticonvulsant and without alteration of its dosage in the three months prior to this study, (iv) without developmental disabilities, (v) without history of addictions or other psychiatric illnesses, (vi) right handedness. Patients were excluded if they had identified epileptic encephalopathies, or had comorbidities including depression, anxiety, attention deficit-hyperactivity disorder rather than cognitive impairment. Other exclusion criteria were diagnosis of tuberous sclerosis, tumours, or major hemispheric deformity (such as hemimegalencephaly and porencephaly), since these lesions preclude the normalization of PET images.

Each patient underwent at least one prolonged (24 hours) EEG monitoring to confirm the localization of the epileptic foci. Video-EEG was performed in five patients who presented difficulties in lesion localization. Tests of Intelligence quotient (IQ), including verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ) were performed by using the Chinese version of the Wechsler Intelligence Scale for Children (C-WISC) or Adults (C-WISA).

PET Imaging with ^{11}C-NMSP and ^{18}F-fluorodeoxyglucose (^{18}F-FDG)

All of the PET imaging studies were done by a clinical PET/CT scanner (Biograph mCT, Siemens Medical Solutions). Dynamic scan was obtained at 0–40 min after a bolus intravenous (i.v.) injection of ^{11}C-NMSP (3.7 MBq/kg) (*11*). A 5-min static brain scan was acquired at 40 min after injection of ^{18}F-FDG (3.7 MBq/kg) (*12*). Interictal PET studies were performed in patients experienced at least 24 hours after the last clinical seizure. A paediatric physician carefully monitored each subject during the entire PET imaging study.

PET Data Analysis

Regions of interest (ROI) were drawn on both hemispheres in the stereotactically normalized images. Voxel-based analysis of asymmetry index (AI) was conducted according to the previous study using SPM8

(*13*). Briefly, AI images were calculated at each voxel according to the following formula: AI = (left - right)/([left + right]/2). In case of the patients with epileptic foci in right hemisphere, the orientation of AI images were flipped along to the sagittal plane. AI images of patients were then compared with the controls, using the two sample t-test of the SPM software package, with an ANCOVA by each subject. Decreased or increased results were regarded as statistically significant if the uncorrected *P* value was under 0.001 (^{18}F-FDG) or 0.01 (^{11}C-NMSP), respectively, with cluster level above 100 voxels.

Statistical Analysis

The results are presented as mean ± SD. All data were analysed by the SPSS (IBM SPSS Statistics, Version 20.0). Analysis of correlation was performed using Pearson's correlation coefficients. Group differences in gender, age, age of onset, duration of epilepsy, MRI abnormality, epilepsy type and IQ were tested using two sample *t*-test or Fisher's exact tests as appropriate. Stepwise multivariate linear regression analysis was conducted to determine the independent contribution of individual variables (gender, age, age of onset, duration of epilepsy, time since last seizure, seizure frequency, lateralization of epileptic foci, epilepsy type, MRI abnormality and combination of anticonvulsant) to the IQ or radiotracer. *P* value less than 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the patients were summarized in **Table 1**. Twelve patients received one type of anticonvulsant, 12 patients received two types, and 1 patient required treatment with three types. All the patients were tested by the C-WISC, except that two patients with ages of 17.5 and 17.7 were tested by the C-WISA. The most frequently used drug was oxcarbazepine (OXC; 16 patients), followed by topiramate (TPM, 9 patients), lamotrigine (LTG; 6 patients), levetiracetam (LEV; 4 patients), valproate (VPA; 3 patients), and clonazepam (CZP, 1 patient). The VIQ (**Fig. 1A**), PIQ (**Fig. 1B**) and FSIQ (**Fig. 1C**) in patients with mono-therapy were significantly higher than those with poly-therapy ($P < 0.01$ in each comparison). However, the VIQ, PIQ, and FSIQ were not influenced by the gender ($P = 0.711$, $P = 0.934$ and $P = 0.879$, respectively), age ($P = 0.812$, $P = 0.948$ and $P = 0.906$, respectively), age of onset

(*P* = 0.856, *P* = 0.757 and *P* = 0.802, respectively), duration of epilepsy (*P* = 0.881, *P* = 0.857 and *P* = 0.837, respectively), time since last seizure (*P* = 0.534, *P* = 0.284 and *P* = 0.450, respectively), seizure frequency (*P* = 0.348, *P* = 0.338 and *P* = 0.424, respectively), lateralization of epileptic foci (*P* = 0.289, *P* = 0.889 and *P* = 0.482, respectively), epilepsy type (*P* = 0.535, *P* = 0.847 and *P* = 0.650, respectively), and MRI abnormality (*P* = 0.884, *P* = 0.638 and *P* = 0.769, respectively).

To determine the independent contribution of individual variables (gender, age, age of onset, duration of epilepsy, time since last seizure, seizure frequency, lateralization of epileptic foci, epilepsy type, MRI abnormality and combination of anticonvulsant) to the IQ, stepwise multivariate linear regression analysis was conducted. Only the combination of anticonvulsant (mono- vs. poly-therapay) was found as the significant contributing variable to FSIQ (B = -28.1; SEM = 8.0; *P* = 0.002).

Monoamine Receptor Activity: between-group Differences (Mono-therapy vs. Poly-therapy)

^{11}C-NMSP bindings in the left (**Fig. 1D**), right (**Fig. 1E**) or entire (**Fig. 1F**) caudate nucleus, were significantly lower in patients with poly-therapy than those with mono-therapy (*P* < 0.05 in each comparison). No significant difference of ^{11}C-NMSP binding was found between the two groups either in the putamen or in pallidum (*P* = 0.085 and *P* = 0.920, respectively). Compared with those of mono-therapy, patients of poly-therapy were detected with significantly lower ^{11}C-NMSP bindings in the right Broadman area 9 (BA9R; **Fig. 2A**), right Broadman area 10 (BA10R; **Fig. 2C**), right Broadman area 32 (BA32R; **Fig. 2E**), right Broadman area 45 (BA45R; **Fig. 2I**), left Broadman area 46 (BA46L; **Fig. 2K**) and amygdala (**Fig. 2G**) (*P* < 0.05 in each comparison).

In these brain regions, combination of anticonvulsant was the only significant contributing variable to ^{11}C-NMSP binding by using stepwise multivariate linear regression analysis (**Table 2**, *P* < 0.05 in each region). However, regarding to the glucose metabolism, there was no significant difference was found in patients with mono-therapy or poly-therapy (*P* > 0.05).

Correlation between Monoamine Receptor Activity and Cognitive Function

Regarding the relationship between regional ^{11}C-NMSP binding and VIQ (**Fig. 1G**), PIQ (**Fig. 1H**), or FSIQ (**Fig. 1I**), significantly positive correlations were found in the caudate nucleus (r = 0.437, r = 0.532 and r = 0.487, respectively, $P < 0.05$ in each comparison); but neither in the putamen ($P = 0.262$, $P = 0.407$ and $P = 0.330$, respectively), nor in the pallidum ($P = 0.305$, $P = 0.853$, and $P = 0.520$, respectively). The ^{11}C-NMSP bindings in BA9R (**Fig. 2B**), BA10R (**Fig. 2D**), BA32R (**Fig. 2F**), BA45R (**Fig. 2J**), BA46L (**Fig. 2L**) and amygdala (**Fig. 2H**) were significantly positively correlated with PIQ (r = 0.453, r = 0.465, r = 0.484, r = 0.447, r = 0.429 and r = 0.414, respectively, $P < 0.05$ in each comparison), but not with VIQ ($P = 0.122$, $P = 0.075$, $P = 0.129$, $P = 0.377$, $P = 0.064$ and $P = 0.201$, respectively). The FSIQ was significantly positively correlated with the ^{11}C-NMSP bindings in BA9R, BA10R, BA32R and BA46L (r = 0.398, r = 0.437, r = 0.397 and r = 0.420, respectively, $P < 0.05$ in each comparison).

Correlation between Monoamine Receptor Activity and Glucose Metabolism

In Patients with Rolandic epilepsy (RE), SPM analysis revealed significant reductions of ^{11}C-NMSP binding in the ipsilateral postcentral gyrus, superior temporal gyrus, lingual gyrus and rolandic operculum ($P_{uncorrected} < 0.01$, cluster size > 100; **Fig. 3A and Table 3**); and found significant hypo-metabolism in the ipsilateral rolandic operculum, superior temporal gyrus, postcentral gyrus and hippocampal gyrus ($P_{uncorrected} < 0.001$, cluster size > 100; **Fig. 3A and Table 4**). Decreased monoamine receptor binding and glucose metabolism were found overlapped in the rolandic operculum, postcentral gyrus and superior temporal gyrus (**Fig. 3A**). The ^{11}C-NMSP binding in the ipsilateral rolandic operculum were significantly positively correlated with glucose metabolism (r = 0.651, $P < 0.05$; **Fig. 3C**).

For the temporal lobe epilepsy (TLE) patients, significant reductions of ^{11}C-NMSP binding were found in the ipsilateral parahippocampal gyrus, inferior and middle temporal gyri ($P_{uncorrected} < 0.01$, cluster size > 100; **Fig. 3B and Table 3**); in addition, hypo-metabolism were presented in the ipsilateral inferior, middle and superior temporal gyri, hippocampal gyrus, fusiform gyrus and rolandic operculum ($P_{uncorrected} < 0.001$, cluster size > 100; **Fig. 3B and Table 4**). Monoamine receptor dysfunction was found overlapped with the glucose metabolic abnormality in the inferior and middle temporal gyri (**Fig. 3B**). ^{11}C-NMSP bindings were significantly positively correlated with glucose metabolism in the ipsilateral

middle temporal gyrus (r = 0.756, *P* < 0.05; **Fig. 3D**) and parahippocampal gyrus (r = 0.855, *P* < 0.05; **Fig. 3E**).

DISCUSSION

We report that cognitive performance significantly positively correlated with the ^{11}C-NMSP binding in caudate nucleus, prefrontal cortex (PFC), dorsal anterior cingulate cortex (dACC) and amygdale. This result suggests that poly-therapy-induced cognitive impairment is related to the reduction of monoamine receptor activity. To the best of our knowledge, this is the first study on the neural correlate between anticonvulsants-induced cognitive impairment and the alteration of monoamine receptor activity or glucose metabolism detected by *in vivo* PET imaging with ^{11}C-NMSP and ^{18}F-FDG in paediatric epilepsy.

Our study demonstrated that in patients with poly-therapy, monoamine receptor activities decreased in the caudate nucleus, PFC (BA9R, BA10R, BA45R and BA46L), dACC (BA32R) and amygdala. This is consistent with the preclinical study on anticonvulsants-induced impaired cognitive function in non-epileptic rats. In which, impaired cognition was found to be attributed to the increased hippocampal 5-HT levels for phenytoin (*14*), but to the decreased hippocampal DA levels for ethosuximide (*15*). However, phenytoin associated elevated monoamine levels in cortex and hippocampus could not justify the associated memory loss in rat model of epilepsy (*16*). These discrepancies might be explained by the suggestion that increased or decreased release of monoamines depends on the concentration of anticonvulsants and the procedure used to evoke neurotransmitter release (*17*). In adult TLE patients, no significant effects of anticonvulsants on 5-HT$_{1A}$R binding were observed by using ^{18}F-FCWAY PET imaging (*18*). It must be noticed that the adverse effect of anticonvulsants on cognition could also be attributed to Na+ channel blockade, enhanced GABAergic activity, or decrement in glutamate-mediated excitation (*19*). Based on the above findings and our results, we speculated that the interaction between multiple anticonvulsants in ion channels and neurotransmitter receptors might aggravate the anticonvulsants-induced cognitive impairment. Since the research on the mechanism of anticonvulsants-induced cognitive impairment is still in its infancy with

many issues that still need to be addressed, elucidation of its mechanism has been appraised as one of the epilepsy research priorities (*20*).

PET imaging in this study indicated that the cognitive performance (VIQ, PIQ, and FSIQ) significantly positively correlated with the ^{11}C-NMSP binding in caudate nucleus. Accumulated evidence has shown that the dopaminergic system, especially D_2 dopamine receptor (D_2DR), is profoundly associated with cognition (*8, 21*). D_2DR make a specific contribution to hippocampus-based cognition by influencing striatum and limbic system, and their interactions (*21*). Another important finding in our study was that ^{11}C-NMSP bindings in PFC, dACC and amygdala were positively correlated with PIQ. Apart from DA, 5-HT signaling at 5-HT_{2A}R also has important effects on several behavioural and cognitive pathways, with the PFC as the central actor (*9*). In addition, activation of the 5-HT_{2A}R in PFC has a modulatory effect on DA neurons, indicating that 5-HT can interact with other modulators of diverse cognitive processes (*22*). Though the amygdala lies at the centre of much of our current thinking about emotion, its role is indeed quite broad and connected with cognitive functions according to amygdala-PFC interactions (*23*). Additionally, the dACC is also supposed to play key role in fundamental cognitive processes, including motivation, decision making, and learning (*24*). Our data further highlighted the crucial role of D_2DR and 5-HT_{2A}R on cognitive function in paediatric patients with epilepsy.

In our current study, significant decreases in VIQ, PIQ and FSIQ were found in patients of poly-therapy compared with those of mono-therapy. This finding is in line with a recent study that each additional drug increased risk of cognitive side effects (*2*). Cessation of anticonvulsants was the strongest predictor of postoperative IQ increase, even after exclusion of patients with continuing seizures (*25*). Therefore, it is recommended that epilepsy patients should be treated with single anticonvulsant wherever possible, and combination anticonvulsants should only be considered when attempts at single anticonvulsant have not resulted in seizure freedom (*26*). Routine cognitive monitoring of anticonvulsants would be highly valuable in order to optimize outcomes and improve adherence to the prescribed medication (*27*). Apart from conventional IQ test, we suggested that ^{11}C-NMSP PET imaging could be one potential evaluation approach for the cognitive monitoring in paediatric epilepsy.

^{18}F-FDG PET imaging of brain glucose metabolism is a well-established and widely available technique for assessment of epilepsy, and the characteristic finding is a regional hypo-metabolism during interictal period. Although hypo-metabolism has been ascribed to factors such as neuronal loss and diaschisis, its underlying neurobiology is not well understood (*28*). In the present study, deceased monoamine receptor activity and glucose metabolism were found overlapped in epileptic foci in patients with RE and TLE. The positive correlation between hypo-metabolism and the reduction of monoamine receptor binding in our study suggested that the abnormal cerebral metabolism might be associated with alterations in neurotransmitters and synaptic activity. The occurrence of epileptic seizures has been explained by an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission. Some other neurotransmitter systems are known to be involved in the epileptogenesis, including DA and 5-HT (*29*). PET studies revealed a reduction of D_2R/D_3R binding in TLE and juvenile myoclonic epilepsy (*30, 31*), and reduction of 5-$HT_{1A}R$ binding ipsilateral to TLE foci (*13*). Our study further demonstrated that 5-$HT_{2A}R$ binding decreased both in RE and TLE patients. This finding is in consistent with the previous report (*32*). 5-HT has an anticonvulsant effect in epilepsy and the 5-$HT_{2A}R$ appear to play a major role. However, further studies are needed to understand the role of 5-$HT_{2A}R$ in epilepsy and its modulation of other neurotransmitter systems.

It is important to acknowledge the potential limitation in this study. Firstly, the baseline cognitive function before anticonvulsants therapy, usually five years ago, was not taken into account in the current study. However, numerous studies have demonstrated that the cognitive impairment may cumulate when anticonvulsants are combined, regardless of the pre-treatment assessment of cognitive function (*2*). Secondly, we did not find significant correlation between cognitive impairment and other clinical variables, including age of onset, duration of epilepsy, and seizure frequency, which might due to the limited numbers in each category.

CONCLUSION

Our findings document that cognitive performance significantly positively correlated with the monoamine receptor binding in caudate nucleus, PFC, dACC and amygdale in paediatric epilepsy.

These results indicated an important role of monoamine receptor dysfunction in anticonvulsants-induced cognitive impairment.

DISCLOSURE

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FIGURE LEGENDS

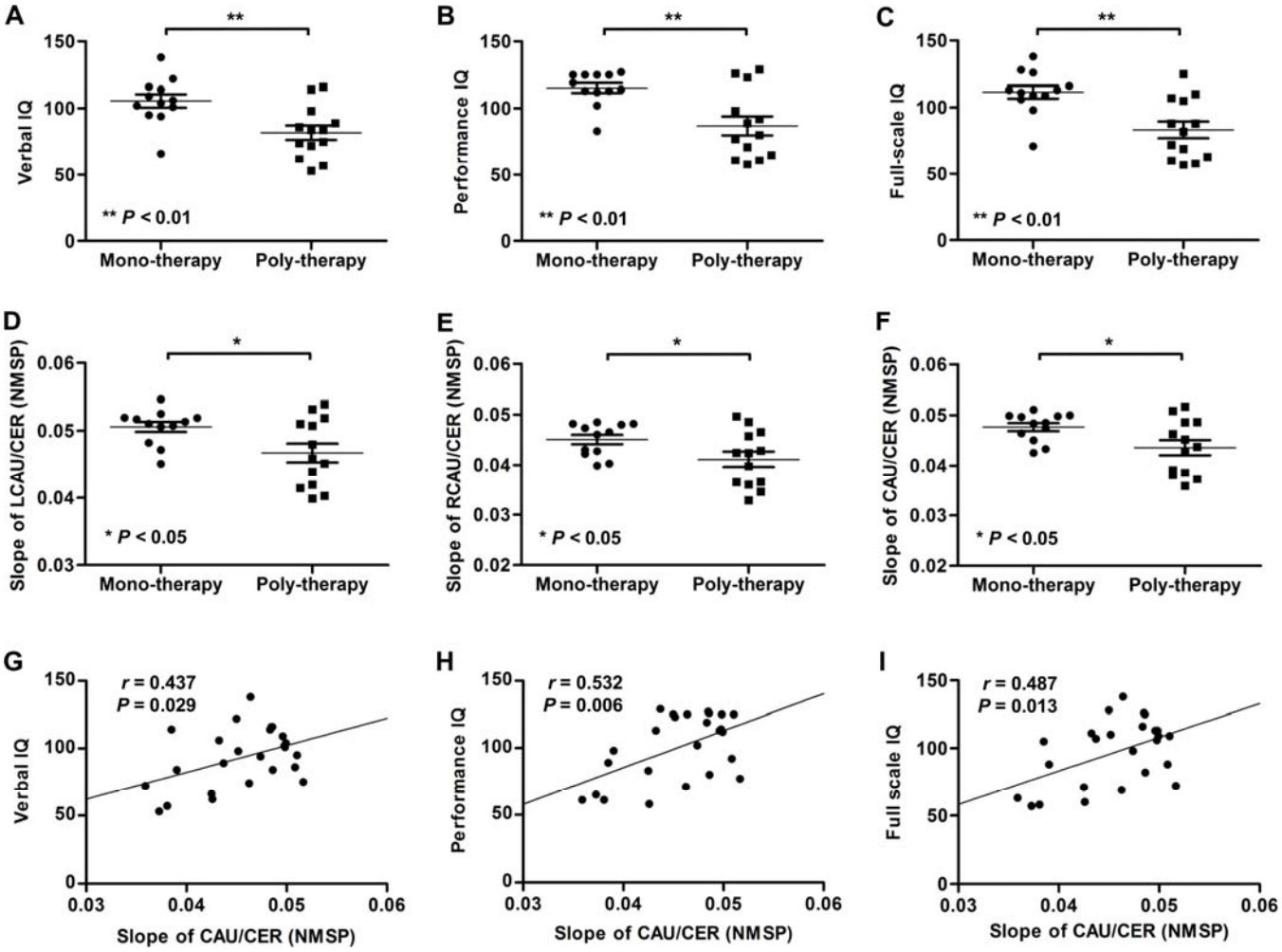

FIGURE 1. Anticonvulsant-induced cognitive impairment and the alteration of monoamine receptor activity in caudate nucleus. **(A-C)** The verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ) were significantly lower in patients with poly-therapy compared with those with mono-therapy ($P < 0.01$ in each comparison). **(D-F)** ^{11}C-NMSP bindings in the left, right or entire caudate nucleus, were significantly lower in patients with poly-therapy than those with mono-therapy ($P < 0.05$ in each comparison). **(G-I)** The VIQ, PIQ, and FSIQ were significantly positively correlated with the ^{11}C-NMSP binding in caudate nucleus (r = 0.437, r = 0.532 and r = 0.487, respectively, $P < 0.05$ in each comparison).

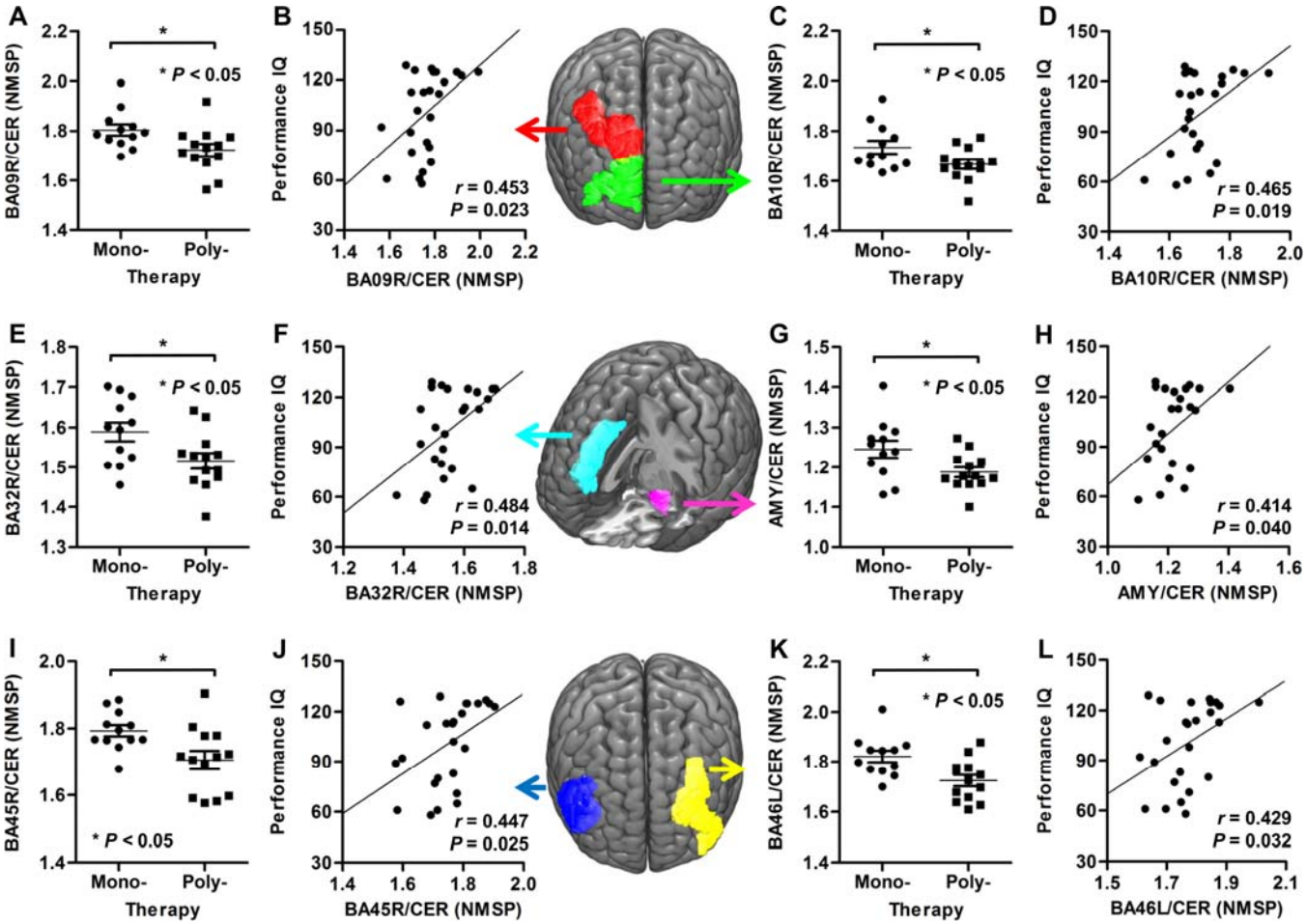

FIGURE 2. Anticonvulsant-induced cognitive impairment and the alteration of monoamine receptor activity in cortex. **(A, C, E, G, I and K)** Patients with poly-therapy were detected with significantly lower ^{11}C-NMSP bindings than those with mono-therapy in the right Broadman area 9 (BA9R), right Broadman area 10 (BA10R), right Broadman area 32 (BA32R), right Broadman area 45 (BA45R), left Broadman area 46 (BA46L) and amygdala ($P < 0.05$ in each comparison). **(B, D, F, H, J and L)** The ^{11}C-NMSP bindings in BA9R, BA10R, BA32R, BA45R, BA46L and amygdala were significantly positively correlated with PIQ (r = 0.453, r = 0.465, r = 0.484, r = 0.447, r = 0.429 and r = 0.414, respectively, $P < 0.05$ in each comparison).

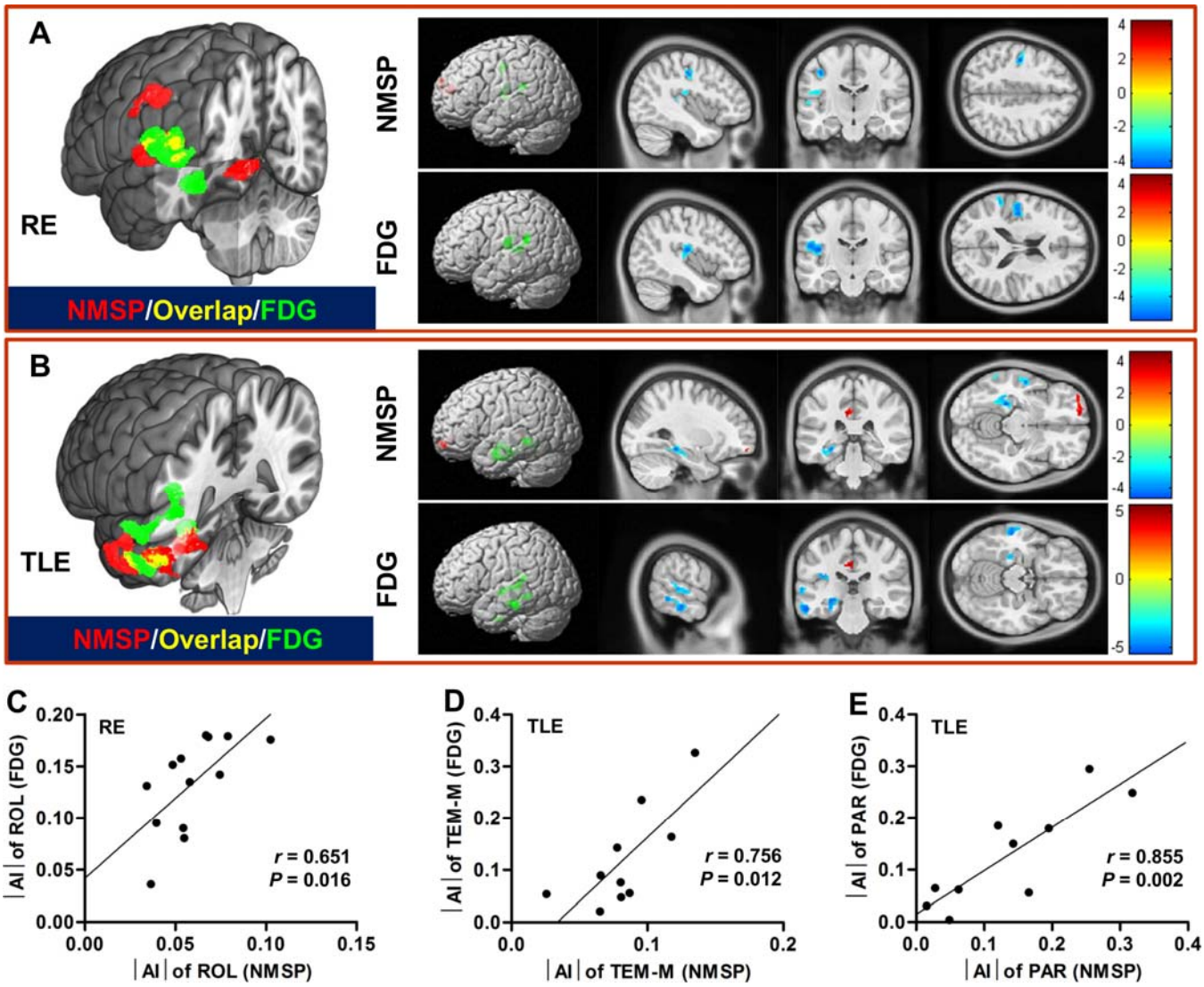

FIGURE 3. Correlation between monoamine receptor activity and glucose metabolism. **(A)** SPM analysis on RE patients revealed significant decreases of ^{11}C-NMSP binding in the ipsilateral postcentral gyrus, superior temporal gyrus, lingual gyrus and rolandic operculum ($P_{uncorrected}$ < 0.01, cluster size > 100), and decreases of glucose metabolism in the rolandic operculum, superior temporal gyrus, postcentral gyrus and hippocampal gyrus ($P_{uncorrected}$ < 0.001, cluster size > 100). Decreased monoamine receptor binding and glucose metabolism were found overlapped in the rolandic operculum, postcentral gyrus and superior temporal gyrus. **(B)** As for TLE patients, significant decreases of ^{11}C-NMSP binding were found in the ipsilateral parahippocampal gyrus, inferior and middle temporal gyri ($P_{uncorrected}$ < 0.01, cluster size > 100), and decreases of glucose metabolism in the ipsilateral inferior, middle and superior

temporal gyri, hippocampal gyrus, fusiform gyrus and rolandic operculum ($P_{uncorrected}$ < 0.001, cluster size > 100). Monoamine receptor dysfunction overlapped with the glucose metabolic abnormality in the inferior and middle temporal gyri. **(C)** In the RE patients, ^{11}C-NMSP bindings in the ipsilateral rolandic operculum (ROL) were significantly positively correlated with glucose metabolism (r = 0.651, *P* = 0.016). **(D and E)** For the TLE patients, ^{11}C-NMSP bindings were significantly positively correlated with glucose metabolism in the ipsilateral middle temporal gyrus (TEM-M) and parahippocampal gyrus (PAR) (r = 0.756, and r = 0.855, respectively, both *P* < 0.05).

TABLE 1 Clinical Characteristics and Comparisons between Mono- and Poly-therapy Groups

Clinical characteristics	Anticonvulsants		*P* value
	Mono-therapy (n = 12)	Poly-therapy (n = 13)	
Gender			
Female / Male	7 / 5	5 / 8	0.434
Age (y)	13.3 ± 1.9	14.1 ± 2.1	0.302
Age of onset (y)	7.6 ± 3.0	8.8 ± 1.9	0.250
Duration of epilepsy (y)	5.7 ± 2.9	5.3 ± 2.2	0.749
Intelligence quotient			
Verbal	105.6 ± 17.5	81.9 ± 19.6	0.004
Performance	115.3 ± 12.7	86.9 ± 25.5	0.002
Full-scale	111.5 ± 16.7	83.4 ± 22.6	0.002
MRI			
Abnormal / normal	2 / 10	2 / 11	1.000
Type of epilepsy			1.000
Rolandic epilepsy	6	7	
Temporal lobe epilepsy	5	5	
Frontal lobe epilepsy	1	1	
Seizure activity			
Resistance / remission	10 / 2	5 / 8	0.041

TABLE 2 Results of Multivariate Linear Regression: Independent Contributions to the Monoamine Receptor Activity (Mono- vs. Poly-therapy)

Brain regions	B	SEM	*P* value
Caudate nucleus	-0.004	0.002	0.029
Amygdala	-0.058	0.024	0.026
BA9R	-0.080	0.034	0.027
BA10R	-0.068	0.032	0.041
BA32R	-0.073	0.031	0.026
BA45R	-0.088	0.033	0.013
BA46L	-0.096	0.033	0.007

B = Beta; BA = Broadman area; L = left; R = right; SEM = Standard error of mean

TABLE 3 Results of SPM Analysis on NMSP Bindings (Epilepsy Patients vs. Control Group)

Regions	Cluster level				Peak level			
	K_E	P (FEW-corrected)	P (FDR-corrected)	P (uncorrected)	P (FEW-corrected)	P (FDR-corrected)	T	Z
Rolandic epilepsy vs. control								
Decreased								
Postcentral	129	0.811	0.756	0.049	0.747	0.650	4.35	3.74
					1.000	0.918	2.70	2.51
Temporal_Sup	125	0.830	0.756	0.052	0.757	0.650	4.34	3.73
					1.000	0.897	2.99	2.75
lingual	114	0.897	0.756	0.062	0.988	0.897	3.75	3.32
					1.000	0.897	3.42	3.08
Rolandic_Oper/Temporal_Sup	143	0.739	0.756	0.039	1.000	0.897	2.99	2.75
					1.000	0.897	2.90	2.67
					1.000	0.951	2.57	2.41
Increased								
Frontal_Sup_Medial/Frontal_Sup	113	0.883	0.573	0.063	0.815	0.282	4.25	3.67
					1.000	0.759	2.78	2.58
Frontal_Mid	141	0.749	0.573	0.040	0.985	0.358	3.78	3.34
Temporal lobe epilepsy vs. control								
Decreased								
Para-Hippocampal/Temporal_Inf	194	0.442	0.325	0.016	0.701	0.656	4.55	3.81
					1.000	0.695	3.54	3.13
					1.000	0.695	3.34	2.98
Temporal_Mid/Temporal_Inf	267	0.197	0.245	0.006	0.836	0.656	4.34	3.67
					0.967	0.656	4.00	3.45
					0.997	0.695	3.69	3.24
Temporal_Mid/Temporal_Inf	139	0.735	0.493	0.037	1.000	0.695	3.24	2.91
					1.000	0.797	3.05	2.76
					1.000	0.839	2.83	2.59
Increased								
Cingulum_Post/Cingulum_Mid	101	0.918	0.672	0.070	0.677	0.718	4.59	3.83
					0.984	0.718	3.89	3.37
Frontal_Sup_Orb/Frontal_Mid_Orb	148	0.684	0.672	0.032	0.961	0.718	4.03	3.47
					0.999	0.718	3.63	3.19
					1.000	0.771	3.24	2.91

FDR = False discovery rate corrected; FWE = Family-wise error; Inf = Inferior; K_E = Cluster size; Mid = Middle; Oper = Operculum; Orb = Orbital; Post = Posterior; Sup = Superior

TABLE 4 Results of SPM Analysis on FDG Uptakes (Epilepsy Patients vs. Control Group)

Regions	Cluster level				Peak level				
	K_E	P (FEW-corrected)	P (FDR-corrected)	P (uncorrected)	P (FEW-corrected)	P (FDR-corrected)	T	Z	
Rolandic epilepsy vs. control									
Decreased									
Rolandic_Oper/Temporal_Sup	602	0.000	0.000	0.000	0.113	0.155	5.55	4.44	
/Postcentral					0.135	0.155	5.47	4.39	
					0.148	0.155	5.42	4.37	
Hippocampal	108	0.041	0.063	0.006	0.349	0.230	4.94	4.09	
Increased									
Cingulum_Mid	100	0.053	0.029	0.007	0.507	0.195	4.69	3.94	
Temporal lobe epilepsy vs. control									
Decreased									
Temporal_Inf/Temporal_Mid	231	0.002	0.003	0.000	0.216	0.316	5.38	4.25	
					0.424	0.341	4.95	4.01	
					0.982	0.759	3.86	3.33	
Hippocampal	128	0.024	0.025	0.003	0.261	0.316	5.27	4.19	
Fusiform	137	0.019	0.025	0.003	0.281	0.316	5.22	4.17	
Temporal_Sup/Rolandic_Oper	366	0.000	0.000	0.000	0.308	0.316	5.16	4.13	
/Temporal_Mid					0.430	0.341	4.94	4.01	
					0.612	0.380	4.66	3.84	
Increased									
Cingulum_Mid	286	0.000	0.001	0.000	0.183	0.329	5.48	4.31	

FDR = False discovery rate corrected; FWE = Family-wise error; Inf = Inferior; K_E = Cluster size; Mid = Middle; Oper = Operculum; Sup = Superior

Supplemental Materials

Alteration of monoamine receptor activity and glucose metabolism in paediatric patients with anticonvulsant-induced cognitive impairment

MATERIALS AND METHODS

Subjects

Intelligence quotient (IQ), including verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ) were assessed using the Chinese version of the Wechsler Intelligence Scale for Children (C-WISC) *(1)*. IQ discrepancy refers to difference between VIQ and PIQ (VIQ-PIQ). Patients were considered to be in "Resistance" if they were failed to achieve sustained seizure free despite adequate anticonvulsants, or to be in "remission" if they had not had any seizures during the last year *(2)*.

Data Analysis

Regions of interest (ROI) for the caudate nucleus, putamen (anterior and posterior), pallidum, thalamus and regional cortex were drawn in both hemispheres in the stereotactically normalized images (**Supplementary Fig. 1A**). The cerebellum was used as a reference region in ^{11}C-NMSP binding analysis as the low density of 5-HT_{2A} and D_2 receptors in this brain region allow for minimal levels of specific binding. The ^{11}C-NMSP PET images between 31 and 40 min, which demonstrated steady ratio of cortex to cerebellum, were selected for the image analysis (**Supplementary Fig. 1B**). In addition, the "ratio index" represents the slope of the striatum to cerebellum ratio over time and is a function of striatal Bmax (**Supplementary Fig. 1C**) *(3)*.

RESULTS

As shown in **Supplementary Figure 2**, significantly negative correlation was found between IQ discrepancy and PIQ (r = -0.472, *P* = 0.017) but not between IQ discrepancy and VIQ (*P* = 0.627). In addition, IQ discrepancy was significantly negatively correlated with ^{11}C-NMSP binding in right Broadman area 45 (BA45R) and Broadman area 46 (BA46R) (r = -0.505 and r = -0.429, respectively,

both $P < 0.05$). Among the 6 patients with significant IQ discrepancy (|VIQ - PIQ | > 15), 5 patients (VIQ – PIQ < -15) were confirmed to have epileptic foci in the left hemisphere, and 1 patient (VIQ – PIQ > 15) in the right hemisphere.

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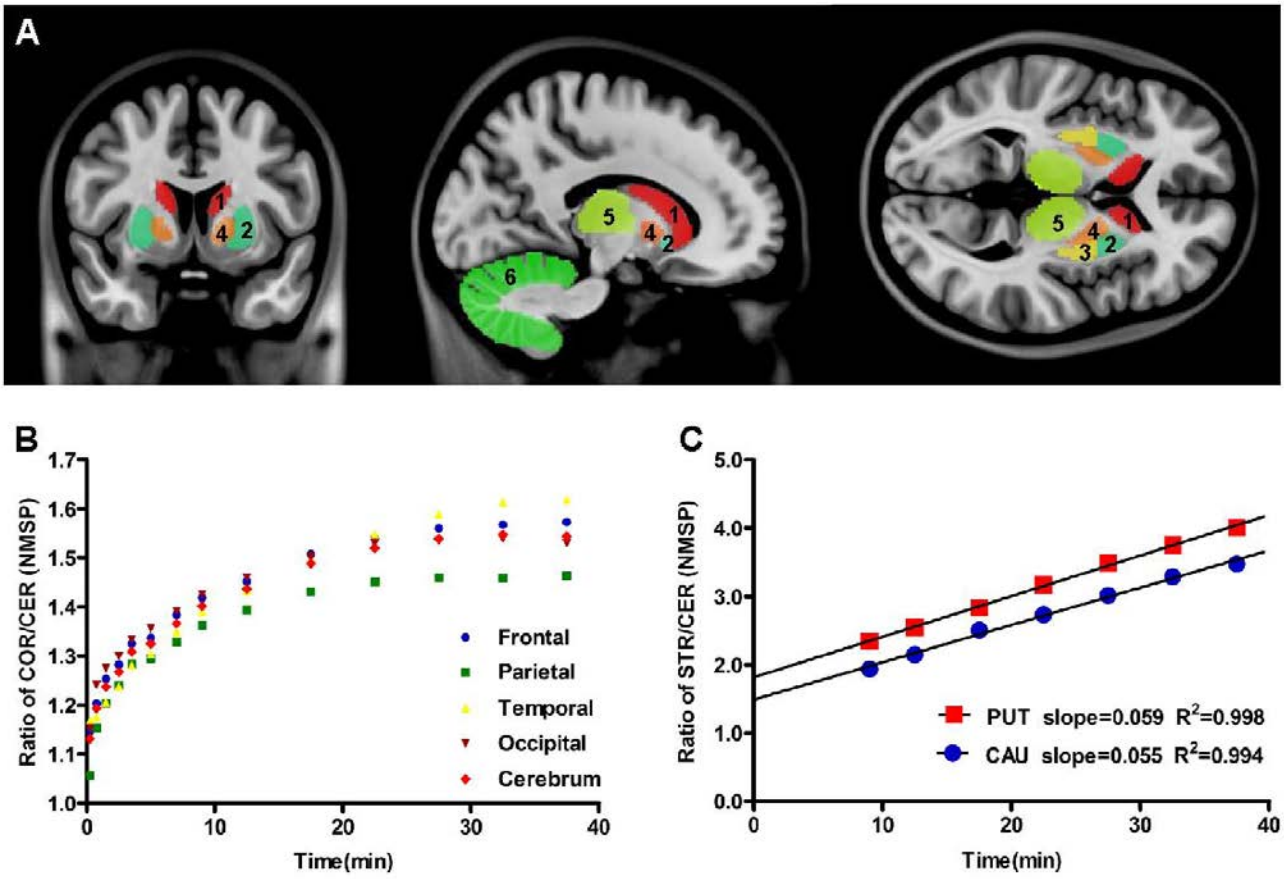
3. Wang GJ, Volkow ND, Logan J, et al. Evaluation of age-related changes in serotonin 5-HT2 and dopamine D2 receptor availability in healthy human subjects. Life sciences. 1995;56(14):Pl249-53.

Supplemental Materials

Supplementary Figure and Legends

Supplementary Figure 1 Region of interest (ROI) and dynamic change of ^{11}C-NMSP binding. **(A)** Outlining of ROIs in caudate (1), anterior putamen (2), posterior putamen (3), pallidum (4), thalamus (5) and cerebellum (6). **(B)** The ^{11}C-NMSP PET images between 31 and 40 min, which demonstrated steady ratio of cortex to cerebellum, were selected for the image analysis. **(C)** The slope of the striatum to cerebellum ratio over time is a function of Bmax.



Supplemental Materials

Supplementary Figure 2 Correlation between IQ discrepancy and ^{11}C-NMSP binding. **(A)** No significant correlation was found between IQ discrepancy and verbal IQ (*P* = 0.627). **(B)** IQ discrepancy was significantly negatively correlated with performance IQ (r = -0.472, *P* = 0.017). **(C and D)** IQ discrepancy was significantly negatively correlated with ^{11}C-NMSP binding in the right Broadman area 45 (BA45R) and Broadman area 46 (BA46R) (r = -0.505 and r = -0.429, respectively, both *P* < 0.05).