SLC63 Gene Polymorphisms is Associated with Striatal Dopamine Transporter Changes after Glucose Loading

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Abstract

We investigated the association between *SLC6A3* gene polymorphisms and changes in dopamine transporter (DAT) availability after glucose loading in humans. An intravenous injection of ^{18}F-FP-CIT was administered after infusion of glucose or placebo, and the emission data were acquired over 90 min in 38 healthy male participants. DAT availability expressed in terms of binding potential (BP_{ND}) was recorded. The 40-bp variable number of tandem repeats (VNTR) in the 3' untranslated region and two single nucleotide polymorphisms (SNPs), rs2652511 and rs2937639, in the *SLC6A3* gene were genotyped. Among the 38 participants, those with a VNTR other than 10R/10R (n = 7) were excluded. The alleles of the two SNPs (rs2652511 and rs2937639) appeared to be inherited together in two fixed combinations (C-G or T-A) in 29 of 31 individuals. The BP_{ND} in the ventral striatum (VST), caudate nucleus, and putamen was not significantly different after glucose or placebo loading according to genotype. However, BP_{ND}s from the caudate nucleus and putamen of all participants with rs2652511 CT/rs2937639 AG (n = 6) were higher after glucose loading. In conclusion, the *SLC6A3* gene polymorphism is associated with the changes in DAT availability after glucose loading. DAT availability after glucose or placebo loading in the VST, caudate nucleus, and putamen did not differ according to the *SLC6A3* genotype.

Introduction

The dopamine transporter (DAT) is a transmembrane protein that actively translocates dopamine from the extracellular space into presynaptic neurons in the dopaminergic system (Vaughan and Foster, 2013). Dysfunction of the DAT has been linked to neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (Roessner et al., 2010), bipolar disorder (Mick et al., 2008), and alcoholism (Du et al., 2011). Additionally, *SLC6A3* gene polymorphisms have been shown to be associated with the expression of striatal DAT (van de Giessen et al., 2009). Among *SLC6A3* gene polymorphisms, most previous studies have focused on the 40-base-pair variable number tandem repeat (VNTR) in the 3' untranslated region of the *SLC6A3* gene. According to a meta-analysis by Faraone et al., a 9-repeat (9R) allele of the VNTR is associated with increased DAT availability in the striatum, independent of the presence of neuropsychiatric disorders (Faraone et al., 2014). However, other *SLC6A3* gene polymorphisms have rarely been investigated.

The brain plays a major role in regulating the energy balance of the body (van Galen et al., 2018). Eating behavior is a process of energy intake, controlled by both the homeostatic and hedonic systems of the brain (Morton et al., 2014; van Galen et al., 2018). The hypothalamus plays a central role in maintaining the physiologic requirements of the body, while the striatum is the major organ that regulates eating behavior through the reward system (Khanh et al., 2014). Regarding neurotransmitters, dopamine plays an important role in reward processing (Wang et al., 2011). However, the DAT is not considered to be involved in the neurobiology underlying eating behavior in humans (Thomsen et al., 2013). Previously, substantial increases in DAT in response to glucose loading were observed, and an important role of DAT

in eating behavior was proposed by Pak et al. (Pak et al., 2020). However, not all individuals showed an increase in striatal DAT availability in response to glucose loading (Pak et al., 2020). Therefore, we hypothesized that *SLC6A3* polymorphisms underlie the changes in DAT availability after glucose loading in humans.

Materials And Methods

Participants

All participants signed an informed consent form prior to participation. Healthy male individuals were included in this study. Heavy smokers; participants with more than a 10% change in weight over six months; and those with a history of drug abuse, brain injury, neuropsychological disorders, or endocrine disorders were excluded. On the day of each visit, the participants were instructed to fast overnight for at least 12 hours and abstain from smoking and alcohol consumption. The participants visited the institution between 11 am and 12 pm to avoid the effect of diurnal variations in dopamine. Twenty-seven participants in this study were included in a previous study of striatal DAT changes after glucose loading (Pak et al., 2020). This study was approved by the institutional review board of Pusan National University Hospital.

Study design

Each participant visited the institution two times, on separate days, for two positron emission tomography (PET) scans. Bilateral antecubital veins were cannulated: one for blood sampling and injection of ^{18}F-FP-CIT, and the other for glucose or placebo infusions. The participants were blinded and randomly assigned to either glucose or placebo infusions. Over 10 min, 300 mg/kg of glucose in a 50% solution was administered. The placebo (normal saline) was also administered at the same speed and volume as the 300 mg/kg of glucose (Haltia et al., 2007). The serum glucose level (mg/dL) and insulin level (μU/mL) were measured before and after the infusion of glucose and placebo. The serum glucose level was determined by using an enzymatic reference method using hexokinase with the Glucose HK Gen.3 (Roche Diagnostics GmbH, Germany). The serum insulin level was determined using an electrochemiluminescence immunoassay method using Elecsys Insulin (Roche Diagnostics GmbH, Germany). An intravenous bolus injection of ^{18}F-FP-CIT (210.9 ± 16.3 MBq) was administered after the infusion of glucose or placebo. The emission data were acquired over 90 min with 50 frames of progressively increasing durations (15 s × 8 frames, 30 s × 16 frames, 60 s × 10 frames, 240 s × 10 frames, and 300 s × 6 frames) using Siemens Biograph 40 Truepoint (Siemens Healthcare, Knoxville, Tennessee, USA). The dynamic PET data were collected in 3-dimensional mode, producing with 148 slices with image sizes of 256 × 256 and pixel sizes of 1.3364 × 1.3364 mm^2. These were reconstructed using filtered back projection with a Gaussian filter.

Genotyping

The DNA of each participant was extracted for genotyping from whole-blood samples. The 40-bp VNTR in the 3' untranslated region and two single nucleotide polymorphisms (SNPs), rs2652511 and rs2937639, in the *SLC6A3* gene were genotyped (van de Giessen et al., 2009). The primers for the VNTR were adopted from those used in a previous study by Vandenbergh et al. (Vandenbergh et al., 1992), and those for the SNPs were designed using Primer3 (v4.1.0, Whitehead Institute for Biomedical Research, Cambridge, MA, USA)(Koressaar and Remm, 2007; Untergasser et al., 2012). Direct sequencing was performed using the Bigdye Terminator v3.1 Cycle Sequencing Kit (ThermoFisher, MA, USA) and the Applied Biosystems 3730XL DNA Analyzer (ThermoFisher, MA, USA).

Image analysis

For a volume-of-interest (VOI)-based analysis, an averaged image (0–10 min after injection) was created from dynamic PET frames and spatially normalized to a ^{15}O-water PET template in Statistical Parametric Mapping 5 (Wellcome Trust Centre for Neuroimaging, United Kingdom). To extract time-activity curves (TACs) of VOIs from full dynamic PET scans, the Oxford-GSK-Imanova striatal atlas from FMRIB Software Library v5.0 (https://fsl.fmrib.ox.ac.uk/fsl) was applied, which is an atlas of the sub-striatal regions of the ventral striatum (VST), caudate nucleus, and putamen segmented according to the anatomical structure, and manually delineated on the non-linear MNI 152 template (Tziortzi et al., 2011). DAT availability, expressed in terms of binding potential (BP_{ND}), was measured by analyzing TACs via the simplified reference tissue method (Lammertsma and Hume, 1996) using the cerebellum as a reference. Image analysis was performed using pmod version 3.6 (PMOD Technologies LLC, Zurich, Switzerland). For a voxel-based analysis, parametric maps were generated for each participant and analyzed using a paired t-test. Results were displayed at a significance threshold of uncorrected $p < 0.0005$ and minimum cluster size for 10 contiguous voxels. Image analysis was performed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) implemented on Matlab R2016b (MathWorks, USA).

Statistical analysis

Normality was assessed using the D'Agostino & Pearson normality test. The Mann-Whitney test was used to compare BP_{ND}s from the VST, caudate nucleus, and putamen after placebo and glucose loading according to genotypes. Wilcoxon matched-pairs signed rank test was used to compare BP_{ND} after placebo and glucose loading separately according to genotypes. A chi-squared test was used to test the difference of frequency in the increase or decrease in BP_{ND}s after placebo and glucose loading according to genotypes. All analyses were conducted using Prism (v7.0d, GraphPad Software Inc, La Jolla, CA, USA).

Results

Thirty-eight healthy men aged 20–31 years were enrolled in this study. After excluding individuals with VNTRs other than 10R/10R (n = 7), 31 participants were categorized according to the rs2652511 and rs2937639 genotypes. The alleles of the two SNPs (rs2652511 and rs2937639) appeared to be inherited together in two fixed combinations (C-G or T-A) in 29 of 31 participants (rs2652511 CC/rs2937639 GG [n

= 1]; rs2652511 CT/ rs2937639 AG (n = 6); rs2652511 TT/rs2937639 AA [n = 23]; rs2652511 TT/rs2937639 GG [n = 1]). To evaluate the effect of rs2652511 and rs2937639 genotypes, 29 participants with rs2652511 CT/rs2937639 AG (n = 6) or rs2652511 TT/rs2937639 AA [n = 23] were included in this study. The characteristics of the participants are shown in Table 1.

Table 1
Characteristics of participants

Variables	rs2652511 CT/rs2937639AG (n = 6)	rs2652511 TT/rs2937639 AA (n = 23)	p
Age (years)	24.0 ± 2.5	24.4 ± 2.7	0.5626
Body mass index (kg/m^2)	21.9 ± 2.2	24.1 ± 3.8	0.1119
BP_{ND}	5.3 ± 1.5	4.5 ± 1.6	0.7331
Placebo loading	2.3 ± 2.1	3.5 ± 1.9	0.2777
VST	4.0 ± 2.0	5.6 ± 2.2	0.3841
Caudate nucleus	4.4 ± 1.8	4.8 ± 1.9	0.2582
Putamen	4.9 ± 2.0	3.7 ± 2.0	0.1925
Glucose loading	6.8 ± 1.6	5.9 ± 2.1	0.1894
VST			
Caudate nucleus			
Putamen			
Data are expressed as mean ± standard deviation.			
BP_{ND}, binding potential; VST, ventral striatum.			

BP_{ND}s in the VST, caudate nucleus, and putamen were compared between participants with rs2652511 CT/rs2937639 AG and rs2652511 TT/rs2937639 AA. BP_{ND} in the VST, caudate nucleus, and putamen was not significantly different after glucose (p = 0.7331, p = 0.2777, and p = 0.3841, respectively) or placebo (p = 0.2582, p = 0.1925, and p = 0.1894, respectively) loading according to the genotype (Fig. 1). rs2652511 and rs2937639 genotypes did not have any effect on the changes in BP_{ND}s in the VST (p = 0.4190, χ^2 = 0.653). However, BP_{ND}s in the caudate nucleus (p = 0.0232, χ^2 = 5.156), and putamen (p = 0.0499, χ^2 = 3.844) of all participants with rs2652511 CT/rs2937639 AG (n = 6) were higher after glucose loading than after placebo loading (Fig. 2). From a voxel-based analysis of participants with rs2652511 CT/rs2937639 AG, significant increases after glucose loading were identified in the right putamen (x, y, z, cluster size: 24, 2, 2, 15 voxels), left putamen (x, y, z, cluster size: -26, 14, 6; -28, 2, 6; 59 voxels), right

caudate nucleus (x, y, z, cluster size: 12, 12, 10; 14 – 2 20; 55 voxels), left caudate nucleus (x, y, z, cluster size: -16, 8, 12; 12 voxels) (Fig. 3).

Discussion

In this study, the DAT availability in the VST, caudate nucleus, and putamen did not differ with the *SLC6A3* genotype (rs2652511; rs2937639). However, changes in DAT availability after glucose loading were affected by the *SLC6A3* genotype (rs2652511; rs2937639). In all participants with rs2652511 CT/rs2937639 AG, striatal DAT availability was increased after glucose loading.

Eating behavior is regulated by both the homeostatic and hedonic systems of the brain (van Galen et al., 2018). The hypothalamus plays a central role in maintaining the physiologic requirements of the body, while the striatum is the major organ that regulates eating behavior through the reward system (Khanh et al., 2014). Among neurotransmitters, dopamine plays a particularly important role in reward processing (Wang et al., 2011). Unlike the dopamine receptor, the DAT, which actively translocates dopamine from the extracellular space into presynaptic neurons (Vaughan and Foster, 2013) was not thought to be involved in the neurobiology underlying obesity in humans (Thomsen et al., 2013) as there was no significant correlation between DAT availability and body mass index (BMI)(Thomsen et al., 2013; van de Giessen et al., 2013; Nam et al., 2018). We have previously highlighted the role of DAT (Pak et al., 2020). In a previous study, substantial increases in DAT availability were observed at least 18% after glucose loading, although the paired t-test of DAT availability between placebo and glucose loading did not find a significant difference (Pak et al., 2020). In addition, BMI was negatively correlated with DAT availability after glucose loading (Pak et al., 2020). In this regard, participants with a lower BMI may have 1) a higher clearance of synaptic dopamine, and 2) a lower endogenous concentration of dopamine due to higher DAT availability, leading to the stop of eating behavior (Pak et al., 2020). According to Jones et al., insulin activates the PI3K/Akt signaling pathway, enhancing the surface expression of striatal DAT in animal studies (Jones et al., 2017). However, not all participants showed an increase in striatal BP_{ND} after glucose loading equally, leading to the insignificant results in paired t-tests (Pak et al., 2020). Therefore, we hypothesized that *SLC6A3* gene polymorphisms may affect the changes in DAT availability after glucose loading.

Dysfunction of the DAT has been linked to neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (Roessner et al., 2010), bipolar disorder (Mick et al., 2008), and alcoholism (Du et al., 2011). Additionally, *SLC6A3* gene polymorphisms have been shown to be associated with the expression of striatal DAT (van de Giessen et al., 2009). Among polymorphisms of the *SLC6A3* gene, most previous studies have focused on the 40-base-pair VNTR in the 3' untranslated region of the *SLC6A3* gene. According to a meta-analysis by Faraone *et al*., the 9R allele of the VNTR is associated with increased DAT availability, and the VNTR has an effect on DAT availability (Faraone et al., 2014). In a study by van de Giessen et al. (van de Giessen et al., 2009), 58.4% (45/77) of the participants had a VNTR of 10R/10R, while this was present in 81.6% (31/38) of participants included in the current study. Ethnic differences may explain this difference in the proportion of the 10R/10R VNTR in each study group. To

rule out the effect of the VNTR on DAT availability, only the 31 participants with the 10R/10R VNTR were included in this study. Previously, only two studies investigated the effects of *SLC6A3* gene polymorphisms other than the VNTR on DAT availability (Drgon et al., 2006; van de Giessen et al., 2009). Drgon et al. screened and identified SNPs of rs2652511 and rs2937639 at the 5' end of the SLC6A3 gene (Drgon et al., 2006). rs2652511 is located in the 5' flanking sequences of the *SLC6A3* gene, while rs2937639 is located in intron 1 of the *SLC6A3* gene (van de Giessen et al., 2009). Participants with rs2652511 C/rs2937639 G had more frequent in highly expressed DAT availability with ^{11}C-cocaine PET (Drgon et al., 2006). However, in a study by van de Giessen et al., neither rs2652511 nor rs2937639 was associated with striatal DAT availability as measured using ^{123}I-β-CIT SPECT (van de Giessen et al., 2009), consistent with the findings of the present study. As we discovered the changes in DAT after glucose loading in humans (Pak et al., 2020), we investigated the association between *SLC6A3* genotypes (rs2652511; rs2937639) and DAT availability after glucose loading. However, the *SLC6A3* genotype did not have an effect on DAT availability after glucose loading. Consistent with two previous studies, rs2652511 and rs2937639 were inherited as fixed allele combinations in 29 of 31 participants (93.5%); either rs2652511 CT/rs2937639 AG (n = 6) or rs2652511 TT/rs2937639 AA (n = 23). In all participants with rs2652511 CT/rs2937639 AG, DAT availability in the dorsal striatum (caudate nucleus and putamen) increased after glucose loading, whereas they were increased in 47.8% (caudate nucleus) and 56.5% (putamen) of participants with rs2652511 TT/rs2937639 AA. Therefore, *SLC6A3* gene polymorphisms (rs2652511; rs2937639) may affect changes in DAT availability after glucose loading according to this preliminary study. However, the changes in DAT availability in the VST were not affected by the *SLC6A3* genotype. The VST and dorsal striatum (caudate nucleus and putamen) are known to have distinct roles. The VST plays a major role in processing reward cues and in the motivation to seek rewards (Caravaggio et al., 2015), while the dorsal striatum (caudate nucleus and putamen) is involved in non-hedonic food motivations of caloric requirements for survival. Therefore, region-dependent DAT regulatory mechanisms (ventral vs. dorsal striatum) might exist in the response to glucose loading reflecting eating behavior.

This study has some limitations. A small number of participants were included in the study. To validate this preliminary study, further studies with larger numbers of participants are needed. To consider the effect of rs2652511 and rs2937639 genotypes, individuals with a VNTR other than 10R/10R were excluded from this study. In addition, a screening procedure might be needed to investigate other candidates of *SLC6A3* gene polymorphisms that have an effect on DAT availability.

In conclusion, we have highlighted that the *SLC6A3* gene polymorphism is associated with the changes in DAT availability after glucose loading. However, DAT availability after glucose or placebo loading in the VST, caudate nucleus, and putamen did not differ according to the *SLC6A3* genotype. Further studies with a larger number of participants are needed to validate this finding.

Abbreviations

DAT, dopamine transporter

BP_{ND}, binding potential

SNP, single nucleotide polymorphisms

PET, positron emission tomography

VST, ventral striatum

Declarations

FUNDING

No

CONFLICTS OF INTERESTS

The authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS

All data are available to corresponding author of the manuscript upon reasonable request.

AUTHOR's CONTRIBUTIONS

Kyoungjune Pak; study design, write the manuscript

Seongho Seo; image analysis

Keunyoung Kim; image analysis

Myung Jun Lee; image analysis, study design

Seong Janng Kim: image analysis

In Joo Kim; write the manuscript

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical permission for the study procedures was obtained from the Institutional Review Boards at Pusan National University Hospital.

Consent to participate

Subject consent has been obtained by Pusan National University Hospital.

Consent for publication

Not applicable.

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stimulation in binge eating disorder', *Obesity (Silver Spring)*, **19**(8), pp. 1601-1608.

Figures

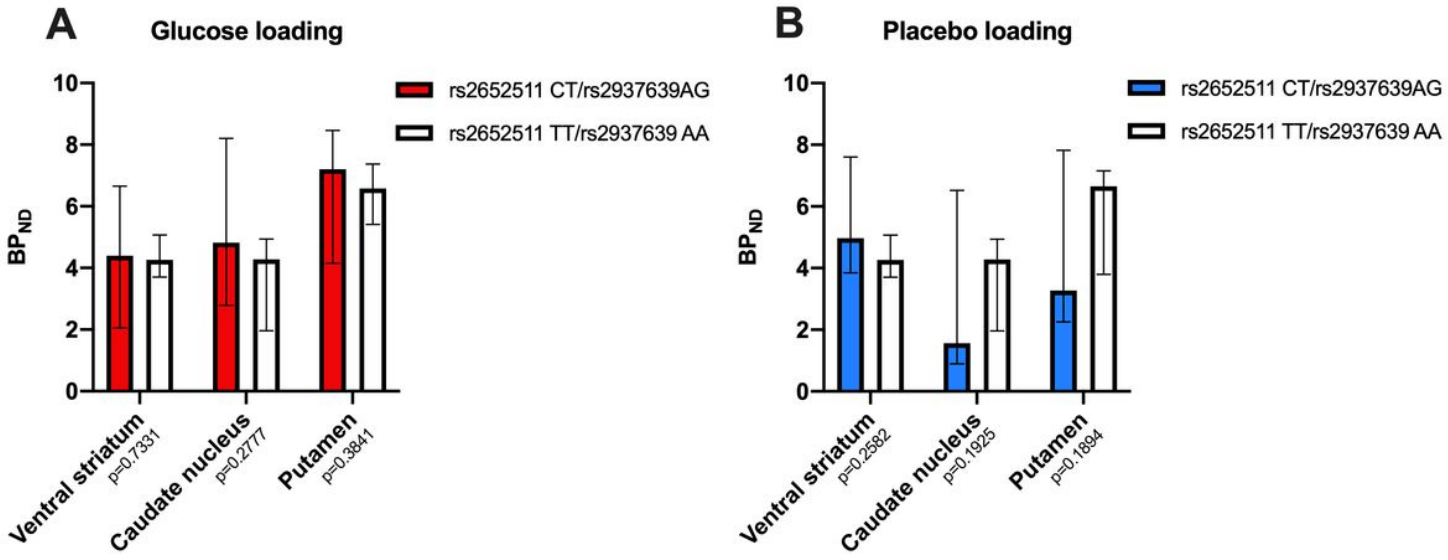

Figure 1

BPND (binding potential) after glucose (A) and placebo (B) loading according to genotype

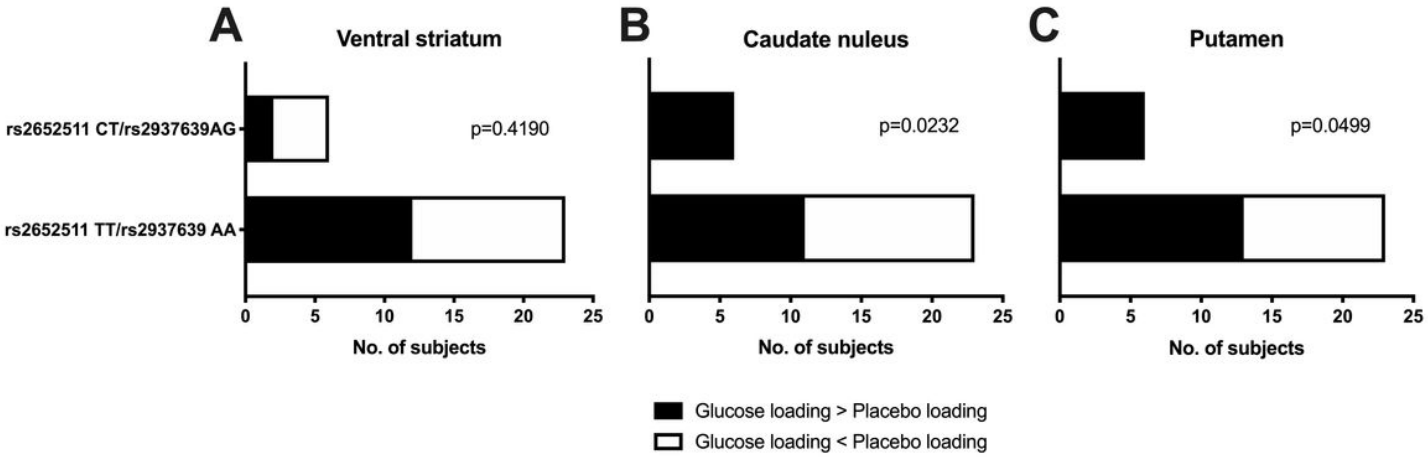

Figure 2

Changes in BPND (binding potential) in the ventral striatum (A), caudate nucleus (B), and putamen (C) after glucose and placebo loading according to genotype

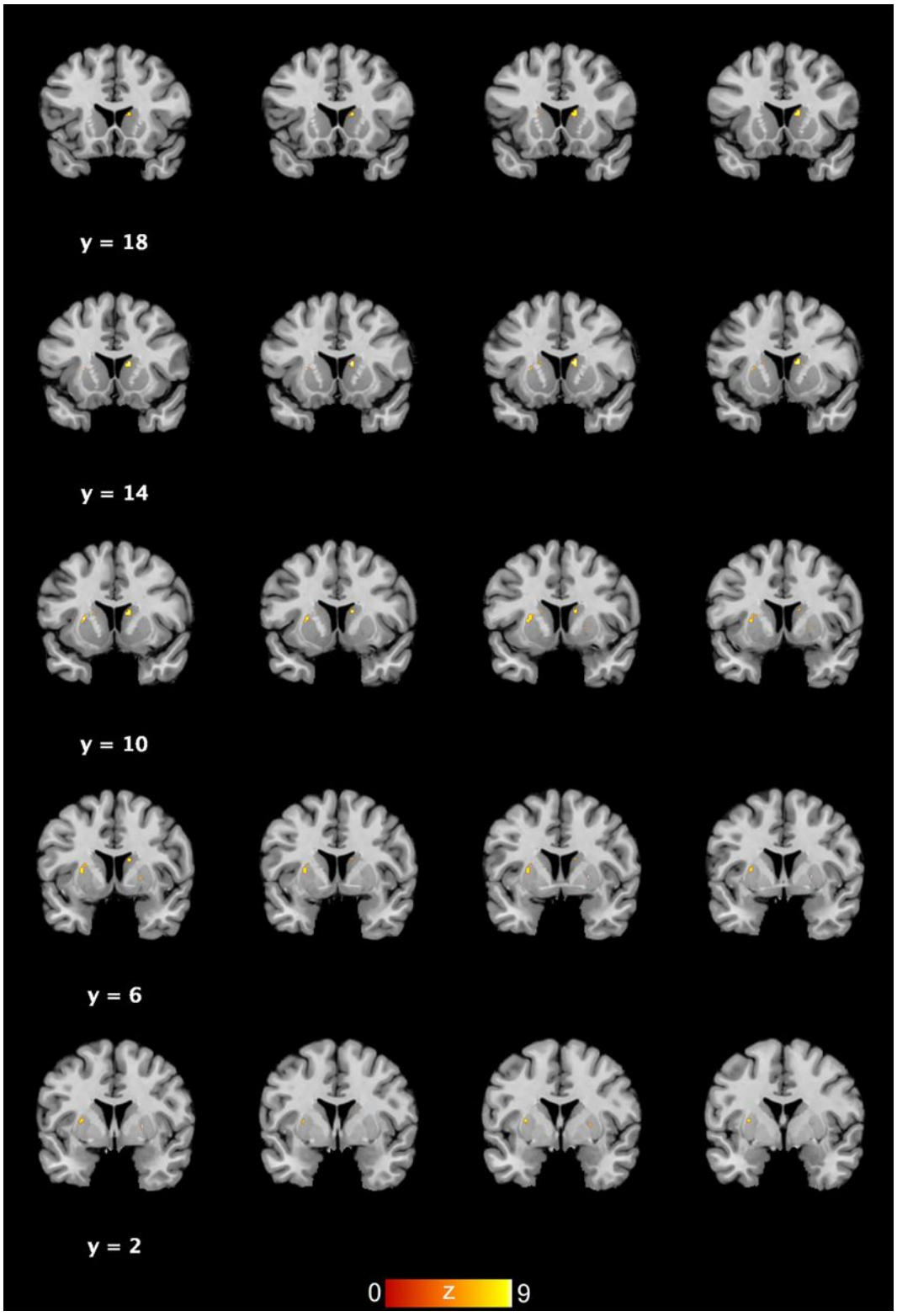

Figure 3

Areas of increased BPND (binding potential) after glucose loading in participants with rs2652511 CT/rs2937639 AG