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Introduction

Since Blood-Oxygen-Level Dependent (BOLD) Functional Magnetic Resonance Imaging (fMRI) was introduced [1], BOLD fMRI has been widely used to investigate the human brain in vivo by measuring regional cerebral blood ow and revealing the underlying neural activity. Recent advances in fMRI allow researchers to study psychiatric disorders with better spatial and temporal resolutions. Consequently, there is growing interests in applying fMRI to psychiatric research [2-9]. fMRI and other functional neuroimaging techniques have demonstrated that resting neural activity and activation during a variety of cognitive tasks are abnormal in schizophrenia [10] in brain regions such as the prefrontal and temporal cortex, cingulate gyrus, hippocampus, striatum, thalamus and the cerebellum [5,11]. Reduced and delayed hemodynamic responses in schizophrenia has been detected by fMRI [11,12] and there is also evidence that people genetically at risk of schizophrenia have changed spatial patterns of brain activity in the face of apparently normal cognition [13,14]. Furthermore, Whalley et al. [15] reported that fMRI technique may identify people in whom the rst symptoms are beginning to emerge [14] which suggest that early treatment may be important.

e caudate nucleus is a sub-cortical region in the striatum that plays an important role in voluntary movement control, memory and learning. It is linked to the frontal cortex and the thalamus through the frontal-striatal-thalamic circuit. Compared with controls, reduced activations in the caudate nucleus in schizophrenia have been reported by a number of fMRI studies in tasks such as prepulse inhibition startle, working memory and learning [4,12,15,16]. Previous studies also indicate that striatal abnormalities occurred in schizophrenia patients and una ected siblings [17].

In order to detect regional BOLD signal changes in the brain, fMRI time course is usually extracted from Regions of Interest (ROIs). One common fMRI ROI analysis is to create small ROIs at the peaks of activation clusters. Another approach is to specify a set of anatomical ROIs (regardless of activation or not) and perform statistical analysis on the fMRI data across these regions [18]. Manual delineation of ROIs is relatively accurate for ROIs such as sub-cortical structures, but manually tracing ROI is time consuming, hard for large sample study and o en lack of reproducibility across di erent tracers or laboratories. In practice, since there can be substantial variability between individuals in anatomy, it requires caution whether the ROI analysis is based on single-subject anatomical atlas or the Talairach atlas [18]. In order to minimize manual intervention, some researchers have suggested other analysis methods such as usi

dedicated Siemens Allegra 3.0-Tesla MRI scanner at the Mount Sinai Medical Center. is study was approved by the IRB at the Mount Sinai School of Medicine. ere was no signi cant di erence in age and sex between the patient and control groups. e fMRI acquisition occurred during an event-related attention-to-prepulse paradigm where the major stimuli were the attended and ignored tones followed by a startle sound. Details of the paradigm are described by Volz et al. [16]. e BOLD imaging was performed using a gradient echo planar (GE-EPI) sequence (28 axial slices, 3 mm thick, skip=1 mm, TR=2s, TE=40 ms, ip angle=90°, FOV=210, matrix=64×64) and the participants underwent six 4.5-min BOLD fMRI scan blocks.

For structural images, a T1-weighted MP-RAGE (Magnetization Prepared Rapid Gradient Echo) was used (208 slices with slice thickness=0.82 mm, matrix size=256×256×208, FOV=21 CM, TR=2500 ms, TE=4.38 ms, TI=1100 ms and an 8° ip angle FLASH acquisition).

Data processing

e following pre-processing was performed on the fMRI data with tools provided by FSL so ware [24]. Motion correction with FSL.MCFLIRT; brain extraction with FSL.BET; mean-based intensity normalization and high-pass temporal ltering (FSL temporal lter, sigma=100.0s).

fMRI ROI analysis were performed in 3 ways: (1) manual ROI approach: caudate ROI was traced on anterior-posterior commissure (ACPC)-positioned individual MRI and applied to the coregistered fMRI images (Figure 1A); (2) semi-automated ROI approach: ROI was traced on the MNI (Montreal Neurological Institute) template with the SNAP program (a semi-automated tracing tool) and applied to each subject's fMRI image that was normalized to the MNI (Montreal Neurological Institute) brain template (Figure 1B); and (3) automated ROI approach: fMRI data were normalized to MNI brain template and stereotactic box-shape ROIs were speci ed with Talairach coordinates (Figure 1C).

To understand the impact of location and size of the automated ROI, pairs of box-based ROIs were placed on the caudate: with center (12, 12, 12), (16, 12, 12), (16, 16, 12), (12, 8, 12) (in Talairach coordinates for the right caudate; and (-12, 12, 12), (-16, 12, 12), (-16, 16, 12), (-12, 8, 12) for the le caudate respectively. For simplicity, the 4 pairs of box-based ROIs are addressed as x12y12, x16y12, x16y16 and x12y8. ree sizes (3×3×3, 5×5×5, 7×7×7) of these box-shape ROIs were de ned with Talairach coordinates to see the impact of automated ROI size. e box-based ROIs were automatically generated by the so ware developed in the Neuroscience PET Laboratory at the Mt. Sinai Medical Center.

e details on how hand-traced ROIs were generated were described in fMRI study [16]. Brie y, the ROIs were traced on the structural MRI and applied to the co-registered fMRI data. e fMRI hemodynamic response time course extracted from these ROIs were averaged over all voxels within the ROIs across all trials.

Statistical analysis

Analysis of Variance (ANOVA) was performed on the time course data extracted from the ROIs. e set up of mixed-design ANOVA was: Group×Condition (attended tone, ignored tone)×Time. Multivariate Wilks and Greenhouse-Geisser epsilon corrections were used to adjust repeated-measures F values on the mean of each ROI. Hemodynamic response curves were drawn under each condition.

e Area Under the Curve (AUC) of hemodynamic response was used to measure the performance of di erent ROIs. AUC was calculated in 4 ways: (1) adding only positive points in the BOLD response curve; (2) adding the root mean square of the points in the curve; (3) adding all points in the curve; (4) adding the absolute values of points in the curve.

Correlations between box-based ROI and hand-traced ROI were computed and t-test between patients and controls was performed on the AUC results.

Results

e Statistical Parametric Map (SPM) in Figure 2 is a comparison between patients and controls. It reveals that schizophrenia patients had less activation in the caudate than controls, which is partially re ected in Table 1.

When comparing the two groups with the Area Under the Curve (AUC) measures, Table 2 indicates that patients have smaller AUC than controls using the manual (signi cant at 1-tailed t-test, p=0.091), semi-automated (not signi cant, p=0.123), and automated ROI (with size 3×3×3, 5×5×5 and 7×7×7 boxes centered at (± 12,12,12), signi cant

Figure 1: Illustration of manual, semi-automated and automated ROI delineation approaches.

A. Manual (hand-traced) ROI (traced on ACPC-positioned MRI) approach (applied to coregistered fMRI).
B. Semi-automated ROI (traced on the MNI brain with SNAP) approach.
& $XWRPDWHG ER[VKDSH 52, VSHFL¿HG LQ WKH 7DODLUDFK VSDFH DSSURDFK

Figure 2: SPM of the contrast of fMRI activation between controls and patients during the attended tone.

The SPM contrast is formed by subtracting fMRI activation of patients from that of controls (Z>1.7, p<0.05, uncorrected). Red clusters in the caudate indicate the higher fMRI activation in controls than patients.

Condition	Measure	Group Mean		t-value	p
		Controls	Patients		
Attend	Mean	0.14	-0.17	1.47	0.155
	Min	-3.05	-2.90	-0.77	0.448
	Max	3.18	2.60	2.76	**0.011**
Attend -Ignore	Mean	0.14	0.04	0.40	0.694
	Min	-2.83	-2.61	-0.94	0.359
	Max	3.05	2.63	1.40	0.176

Mean: averaged z-value in the caudate; Min: minimal z-value in the caudate; Max: maximal z-value in the caudate.

Table 1: t-test between patients and controls of Z-values in the caudate in SPM.

Condition	Measure	Manual	Semi-Auto	Auto (Size:7 center (± 12, 12, 12))
Attend	Positive AUC (Pos_AUC)	-0.23	-0.05	-0.54
	Root mean square (RMS)	-0.15	0.06	-0.06
	All AUC (All_AUC)	-0.31	-0.16	-0.58
	Absolute AUC (Abs_AUC)	-0.04	0.10	0.13
P336tiv9	AUC (Pos_AUC) -0.58			
Attend				

at 1-tailed t-test, p=0.077, 0.063 and 0.053) approaches measured by Root Mean Square (RMS). e results of e ect size are consistent with t-test results (Table 2).

e correlations between manual and semi-automated, manual and automated ROI approaches (included size 3×3×3, 5×5×5 and 7×7×7 boxes) are listed in Table 3. One can see that the correlation of area under the hemodynamic response curve (AUC) between manual and semi-automated approaches is signi cantly high (R=0.81-0.96),

functional neural networks [25]. Since the caudate is linked with the frontal-striatal-thalamic circuitry, abnormal hemodynamic response in the caudate in patients with schizophrenia may re ect the functional de cits (e.g., attention impairment) in their frontal-striatal-thalamic circuitry. Such ndings have been reported and further discussed by Hazlett et al. [17,26].

e rest of the ndings in this study are related to the 3 ROI methods and all of them are based on anatomical ROIs. ere are arguments on the weakness and strengths of anatomical ROIs vs. Functional ROIs (fROIs) in fMRI studies. In a pharmacological fMRI study [25,26], compared the anatomical and fROIs and found that the anatomical ROI (combined with an index of top 20% voxels of activation) was more reliable than the fROI approach in detecting the experimental e ect [26]. In addition, they concluded that fROIs should be used with caution because the use of fROIs from individual sessions introduced unacceptable biases in the results, while the use of union fROIs yielded a lower sensitivity than anatomical ROIs [26,27]. However, when studying resting-state fMRI with functional connectivity measures and introducing a data-driven method for generating an ROI atlas by parcellating whole brain resting-state fMRI data into spatially coherent regions of homogeneous functional connectivity, Craddock et al. [28] found that the evaluated anatomical atlases showed poor ROI homogeneity which failed to reproduce functional connectivity results accurately [27]. ese studies indicate that it may be appropriate to use anatomical ROIs for fMRI studies on hemodynamic response and activation, and use fROIs for studies on functional connectivity.

Despite the obvious di erences in shape, size and di erent registration space between the manual and semi-automated ROI approaches, the two methods had signi cantly high ($p<0.05$) correlations, and detected smaller AUC of fMRI hemodynamic response in schizophrenia patients than controls (with RMS measurement), which suggests that the two methods extract similar time course from the fMRI data. However, there was relatively low correlation in the AUC between hand-traced ROI and box-based ROI (x12y12) with size 7×7×7 voxels and signi cant group di erence for the box-based ROI. is can be explained by comparing the ROI locations in Figure 1 and the activated regions in the caudate in Figure 2 (SPM with contrast for e ect of control - patient at group level). Figure 2 reveals that the di erences in BOLD activations between control and patient groups are not uniformly distributed within the caudate which may be caused by the non-uniform BOLD signal distribution in the caudate of both groups. Since the box-based ROIs are located in the caudate regions which cover more signi cantly activated voxels, while the hand-traced ROI contains the whole caudate volume including the insigni cantly activated regions, the time course extracted from these box-based ROIs re ected the averaged fMRI hemodynamic response of most signi cantly activated voxels within the ROI, while the time course extracted from the hand-traced ROI re ected an average of the hemodynamic response of mostly insigni cantly activated voxels. erefore, the averaged BOLD signal was stronger (i.e., the di erences of BOLD signal between controls and patients are bigger) in these automated box-based ROIs than that of manual (hand-traced) ROI and such box-based ROIs are more sensitive in detecting group di erences than manual ROI in group t-test. e non-uniformity of

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