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See next page for additional authors
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A Positron Emission Tomography Study of Brain Activation in Chinese-Speaking Stutterers

Feng-Chu Tseng,1 Jung-Lung Hsu,2,7 Yen-Kung Chen,3,4 Lin-Fen Hsieh,1,4 Hung-Che Wang,5 Fa-Shun Tsai,6 Ya-Ling Chao1

Departments of 1Physical Medicine and Rehabilitation, 2Neurology, 3Nuclear Medicine, and 6Center of Positron Emission Tomography, Shin Kong Wu Ho-Su Memorial Hospital, Taipei; 4School of Medicine, Fu Jen Catholic University, Taipei; 5Institute of Brain Science, National Yang-Ming University, Taipei; 7Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei.

Background/Purpose: Although neuroimage studies on English-speaking stutterers have been reported previously, there was few positron emission tomography (PET) study of brain activation in Chinese-speaking stutterers. The purpose of this study was to investigate brain activation patterns in stutterers who speak Chinese.

Each subject was scanned via using a PET scanner with a [18F] deoxyglucose marker. The stutterers group received two separate PET scans, one during solo reading (stuttering condition) and the other during choral reading (fluent condition). The normal speakers had only one scan following solo reading.

Significant statistical difference in brain activation between the stutterers during solo reading and normal speakers was observed (p<0.05). For stutterers during solo reading, PET showed right-lateralized activation in the superior frontal gyrus (Brodmann area or BA 11), middle frontal gyrus (BA 8, 9), inferior frontal gyrus (BA 45-47), postcentral gyrus (BA 1-3, 43), and superior temporal gyrus (BA 22). Comparison between solo reading and choral reading in stutterers disclosed significantly more activation in the bilateral medial frontal gyrus (BA 6, 9-11, 21), bilateral cingulate gyrus (BA 24, 31-33), bilateral parahippocampal gyrus (BA 27, 36), left precentral gyrus (BA 4), left caudate body, and right caudate tail.

In conclusion, PET study showed over activation of right brain structure (or under activation of left brain), including the motor cortex and primary auditory cortex, in stutterers who speak Chinese. The findings were similar to those in stutterers who speak English, and may indicate deficit in verbal fluency circuit and lack of normal self-monitoring of speech. (Tw J Phys Med Rehabil 2012; 40(1): 9 - 17)

Key Words: stuttering, PET, Chinese

INTRODUCTION

Stuttering is a worldwide problem and is found in all languages. The incidence of stuttering is about 5%, and the prevalence is 1% in school-age children, with a male-to-female ratio of 3:1.1-3 The causes of stuttering are unknown. Travis thought that lack of dominance in
left hemisphere might be the cause of stuttering. Bloodstein suggested that stuttering was due to the psychological expectation and conflict. Perkins et al proposed that speech involves linguistic and paralinguistic components, each of which is processed by a different neural system; when they are dysynchronous and under time pressure, stuttering develops.

Recent advances in functional imaging studies including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have yielded important insights into the neural systems underlying the mechanism of stuttering. Previous PET regional cerebral blood flow (rCBF) study found normal speakers showed bilateral (left>right) activation of primary sensorimotor cortex during both solo and chorus reading conditions, while the stutterers showed increased activation during the solo reading and markedly reduced activation during the chorus reading in the supplementary motor area (left>right) and the superior lateral premotor cortex (right>left). Based on a PET study of 4 adult stutterers, Wu et al also proposed that stuttering may arise from a defect in functional neuroanatomical circuit.

A review of PET studies and other imaging research draw several conclusions: (1) overactivated right hemisphere during stuttering, especially those structures homologous to those in left hemisphere used by normal speakers, e.g. the right frontal operculum, similar to Broca’s area in the left hemisphere; the right insula, similar to left insula, which may function as a connection between Wernicke’s area and Broca’s area; (2) inactivity of left auditory cortex during stuttering, that is, while stuttering, patients are not using auditory feedback to monitor and control their speech; (3) neuroanatomical differences between stutterers and normal speakers. Stutterers have larger right planum temporale while normal speakers have larger left planum temporale; additionally, fibers in the left operculum in stutterers were less dense than those of normal speakers; (4) right hemisphere over-activations are reduced and cortical activity is more left-lateralized followed by fluency improvement.

Although neuroimage studies on English-speaking stutterers have been reported previously, as far as we know, there has never been any PET study of brain activation relating to Mandarin Chinese-speaking stutterers. The Mandarin Chinese writing system differs markedly from alphabetic languages such as English in orthography and phonology. Previous neuroimaging studies demonstrated that brain activation during reading aloud of Mandarin Chinese characters was bi-lateralized and the peak activation was in the left middle frontal lobe, the Brodmann area (BA 9), which were rarely found in studies about the processing of alphabetic language.

Because written Chinese is quite different from alphabetic languages in orthography and phonology, we hypothesized that the neural mechanisms of Mandarin Chinese-speaking stutterers may differ from those of English-speaking (or other alphabetic-language speaking) stutterers. Cross-linguistic comparisons could shed light on the understanding of the brain mechanisms of stuttering. We aimed at investigating the brain activation in Mandarin Chinese-speaking stutterers via using PET scanning.

**METHODS**

**Study subjects**

Four healthy dextral men (mean age 30.8 years, range 23 to 42 years) with developmental stuttering and four dextral male normal speakers (mean age 26.8 years, range 25 to 28 years) participated in this study (Table 1). All of the stutterer subjects were recruited from the outpatient clinic of Physical Medicine & Rehabilitation in a teaching hospital and the normal subjects were from the hospital staff. There were no significant statistical differences in age, gender, education duration, and family history of stuttering between both groups; however, significant statistical difference in number of SLD (stuttering-like disfluency) was found between both groups (P value = 0.03). All participants were native speakers of Mandarin Chinese (official language of Taiwan and China) and were screened for a negative history of neurological, psychiatric, hearing, or other medical disorders that might affect brain function.

Weighted SLD was used to evaluate the presence and severity of stuttering. SLD encompasses part-word, monosyllabic word repetition, disrhythmic phonation, and tense pause. All subjects were evaluated by a speech pathologist who has more than 15 years’ experience in the clinical management of stuttering.
arranged to have a talk with the speech pathologist for one hour, and stuttering was defined by presence of at least 4 SLDs in 100 Mandarin words. Although 10 male stutterers were screened initially, 6 subjects were excluded due to less than 4 SLDs in the solo reading condition during PET scan. That is, 4 stutterers served as the experimental group. All subjects gave informed consent approved by the Hospital Ethics Committee.

**Procedure**

Each subject was scanned using a PET scanner (Siemens/Cti Ecat HR+) with a \([^{18}\text{F}]\) deoxyglucose (FDG) marker. The FDG marker allowed for an integrated view of the metabolic actions that underlined the speech process during the non-stuttering or fluent condition. For improving fluency in the non-stuttering speaker, chorus reading is frequently used. In this study, the stutterers read a paragraph with a tape during chorus reading, which represented stuttering condition. On the contrary, the stutterers often exhibit stuttering during solo reading (reading by himself or herself), which represents stuttering condition. All subjects received instruction in solo or chorus reading. Thirty seconds before FDG injection, the reading task started.

The experimental group received two separate PET scans, one during solo reading and the other during chorus reading. Each reading lasted for 20 minutes, and each scan took about 90 minutes. The first and the second scans were separated by at least 24 hours. The normal speaker had only one scan during solo reading. All subjects (stutterers and normal controls) were required to fast for at least 8 hours before the PET scan; furthermore, all subjects were supposed to be well hydrated and avoid strenuous work or exercise for 24 hours prior to the scan.

**Image Acquisition**

PET scans were acquired on an ECAT HR+ PET scanner (Siemens, model 962, Knoxville, TN) in three-dimensional (3D) mode [63 transaxial planes, 2.4-mm thickness; in-plane resolution = 4.1 mm full-width at half-maximum (FWHM) over a 15.2-cm field of view].

Each frame was rebinned to 2D data set by Fourier rebinning. Then, the frames were reconstructed by order subset expectation maximization (OSEM) method with an FWHM 3mm Hann filter. The reconstructed dynamic frames were summed after they were viewed in a cine viewer to verify that there were no motion artifacts. Any frame with evidence of motion was excluded from summing.

Transmission images were obtained for 5 minutes to correct for photon attenuation using a germanium 68 line source. After IV administration of 296 MBq (8 mCi) of FDG, emission images were acquired for 20 minutes. The uptake period between FDG injection and the beginning of the emission scan was 60 minutes. Accurate positioning of the patient between transmission and emission scans was performed using laser marks.

**Data analysis and statistical analysis**

For comparison of demographic data between stutterers and normal controls, Mann-Whitney U-test was used for continuous variables, and Fisher’s exact test was performed for family history of stuttering. PET images were reconstructed using standard procedure, and the input blood flow images were anatomically normalized using the coordinating of Talairach atlas. Locations of images were expressed as millimeter coordinates referenced to the anterior commissure as origin, the right, superior, and anterior being positive. Anatomical labels and BA designations were also applied. The analyzed regions included the cortical and subcortical areas of the brain. Wilcoxon signed-rank test was performed for comparison between solo-reading condition and chorus-reading condition in stuttering subjects. Additionally, statistical parametric mapping (SPM) analysis was performed for voxel-based analysis. The raw PET images were first converted to analyze formats from their native image formats using MRlcro software developed by Chris Rorden. Each individual image was then re-oriented and spatially normalized to the standard Montreal National Institute (MNI) template included in SPM2 using a 12-parameter affine transformation. Then, non-linear SPM algorithms (7x8x7, 12 non-linear iterations with moderate nonlinear regularization) were used to spatially normalize each subject’s image to the SPM PET template. As a result, each subject’s image was re-sampled into 2x2x2 mm voxels in a cube with axes right-left, anterior-posterior, and superior-inferior, respectively. Then, a 3-D Gaussian filter (8 mm width) was utilized to smooth each image. The mean intensity of each image was scaled to 50 for
each subject. Wilcoxon signed-rank test comparisons (choral reading and solo reading) were performed on a voxel-by-voxel basis using a general linear model based on the theory of Gaussian fields,[13,14] within SPM. The first comparison sought areas of increased perfusion and the second was for areas of decreased perfusion. The resulting set of voxel values for each comparison constituted a statistical parametric map or SPM{t}. The SPM{t} maps were then transformed to unit normal distribution, SPM{z}. The significant voxels were defined as those surviving a probability threshold of $P < 0.05$ after correction for multiple comparisons and the contiguous clusters of >15 voxels (120 mm$^3$). In between-group comparisons (stutterers in solo reading vs normal speakers), significant voxels were defined as those surviving a probability threshold of $P < 0.05$ after correction for multiple comparisons and the contiguous clusters of >15 voxels (120 mm$^3$). SPM results on the Mann-Whitney U test and between group analyses were then overlaid on a normalized PET image.

**RESULTS**

Significant statistical difference in brain activation between the stutterers and normal speakers during solo reading was observed (Table 2, Figure 1). For stutterers during solo reading (stuttering condition), right-lateralized activation in the superior frontal gyrus (BA11), middle frontal gyrus (BA 8, 9), inferior frontal gyrus (BA 45-47), postcentral gyrus (BA 1-3, 43), and superior temporal gyrus (BA 22) was shown.

In comparison between solo reading and chorus reading in the stutterers, significantly greater activation during solo reading in the bilateral medial frontal gyrus (BA 6, 9-11, 21), bilateral cingulate gyrus (BA 24, 31-33), bilateral parahippocampal gyrus (BA 27, 36), left precentral gyrs (BA 4), left caudate body, and right caudate tail was demonstrated (Table 3, Figure 2).

**DISCUSSION**

This study demonstrated significant differences in brain activation between the stutterers and normal controls in solo reading (stuttering condition) and between the solo reading and chorus reading in the stutterers. Over-activation of the right brain, including superior and middle frontal gyrus (BA 8, 9, 11), inferior frontal gyrus (BA 45-47), postcentral gyrus (BA 1-3, 43), and superior temporal gyrus (BA 22) was found in the Mandarin Chinese-speaking stutterers. The findings were basically similar to those of previous studies on English-speaking stutterers. As far as we know, this study is the first report on PET imaging research in Mandarin Chinese-speaking stutterers.

Fox et al found that in normal controls, paragraph reading activated the primary motor cortex for the mouth (BA 4), supplementary motor area (BA 6), inferior lateral premotor cortex (BA 6, 44), anterior-temporal extra-primary auditory cortex (BA 2, BA 21, 22), the visual system, and the cerebellum. [15] Activations were predominantly left-lateralized except the visual system and cerebellum, which were activated bilaterally. However, during stuttered reading, extensive hyperactivity of the cerebral and cerebellar motor systems with right lateralization of primary and extrapyramidal motor cortices was shown. Compared with normal controls, Wu et al also demonstrated hypoactivity of the left caudate in the stutterers during solo reading, and remained hypoactive even during fluency induction using chorus reading. Our study did not demonstrate significant difference in the activation of the cerebellum and left caudate between the stutterers and normal control in the solo reading condition; however, other findings were basically consistent with the previous studies in English-speaking stutterers.

There are two possible explanations for these over-activated right hemisphere structures during stuttering. One explanation is that during embryonic stage, the right side of the brain becomes “wired” to be the primary speech and language area.[16] Some difficulties in speech development may be due to the fact that the right brain is not usually suited for speech production. As the child grows older, more complicated speech contents are required and stuttering develops. Another explanation is the compensation mechanism. In subjects with stuttering, the right brain becomes active only when the left brain fails to function well for speech production.[17]

This study displayed inactivation or hypoactivation of the left primary auditory cortex. (Table 2) In Fox’s study, normal speakers showed activation of bilateral auditory cortex (BA 2, 21, 22), with left lateralization.
However, in stuttering condition, inactivation of the left superior temporal cortex and left posterior temporal cortex (BA 22) was detected in stutterers. These findings suggest the possibility that when subjects stutter, they are not using auditory feedback to monitor and control their speech. Furthermore, deactivation of left inferior frontal cortex (BA 47) was also found in our study and in Fox’s report. Fox suggested that a circuit between left frontal cortex (BA 47) and left temporal cortex (BA 22) is related to verbal fluency; therefore, deactivation in these two areas may contribute to stuttering. Additionally, the use of different fluency-inducing strategies, such as chorus reading, singing, or metronome-trained speech appears to normalize the focal activations in the motor-auditory region.

This study also showed deactivation of the left superior temporal cortex (including Wernicke’s area), which was also found in Fox’s study. Wernicke’s area may be important for storing the phonological representations of words, and activation of this region may be a key stage in phonological planning for speech production. Lack of activation during stuttering may reflect a deficit in the sequence of phonological selection, phonetic planning, and motor execution.

Our study displayed that in stuttering condition (solo reading), the stutterers showed greater activation in bilateral cingulate gyrus (limbic system) than in non-stuttering condition (chorus reading). The cingulated gyrus was subdivided into ‘affect’ and ‘cognition’ components. The affective division of cingulated cortex modulates autonomic activity and internal emotional response, while the cognitive division is engaged in response selection associated with skeletomotor activity and response to noxious stimuli. The limbic system acts as the emotion modulator. When stutterers feel anxious during stuttering condition, the limbic system becomes activated.

Stuttering not only interferes with communication, but also exhibits negative communication attitudes, and less satisfactory quality of communication. Even the causes of stuttering are still unknown, PET or other functional neuroimaging studies have provided new insights into the neural process for developmental stuttering. Observed differences in functional brain mapping between stutterers and normal speakers, and between fluent and disfluent speech in the stutterers have allowed researchers to develop specific hypotheses with regard to neural deficit underlying the development of stuttering. These findings also help the clinicians to design skills for facilitating fluency, and thus possibly change the underlying neural process of stuttering.

Table 1. Characteristics of subjects

<table>
<thead>
<tr>
<th>Cases</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Education (yrs)</th>
<th>Family history of stuttering</th>
<th>SLD* (0-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stutterer</td>
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<td>Male</td>
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<td>9</td>
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</tr>
<tr>
<td></td>
<td>2</td>
<td>Male</td>
<td>27</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Male</td>
<td>27</td>
<td>13</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Male</td>
<td>25</td>
<td>16</td>
<td>No</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
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<td>12</td>
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<td></td>
<td>2</td>
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<td>30</td>
<td>13</td>
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</tr>
<tr>
<td></td>
<td>3</td>
<td>Male</td>
<td>28</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Male</td>
<td>42</td>
<td>9</td>
<td>No</td>
</tr>
</tbody>
</table>

Note: No significant statistical difference between the stutterers and normal controls with regard to gender, age, education duration, and family history of stuttering. Significant statistical difference in number of SLD (P value = 0.03) between both groups.

Abbreviation: SLD, stuttering-like disfluency.
* SLD per 100 Mandarin Chinese words.
Table 2. Brain regions showing significant differences between stutterers in stuttering condition and normal controls

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>BA</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t</th>
</tr>
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<tbody>
<tr>
<td>Inferior frontal gyrus</td>
<td>R</td>
<td>45</td>
<td>50</td>
<td>18</td>
<td>6</td>
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</tr>
<tr>
<td></td>
<td>R</td>
<td>46</td>
<td>42</td>
<td>38</td>
<td>14</td>
<td>5.0377</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>47</td>
<td>38</td>
<td>26</td>
<td>4</td>
<td>3.457</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>R</td>
<td>1</td>
<td>68</td>
<td>-20</td>
<td>24</td>
<td>2.5492</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>2</td>
<td>66</td>
<td>-24</td>
<td>24</td>
<td>4.6482</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>3</td>
<td>66</td>
<td>-12</td>
<td>26</td>
<td>2.6368</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>43</td>
<td>64</td>
<td>-6</td>
<td>10</td>
<td>4.7396</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>R</td>
<td>8</td>
<td>54</td>
<td>14</td>
<td>42</td>
<td>4.5107</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>9</td>
<td>56</td>
<td>12</td>
<td>40</td>
<td>3.7078</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>R</td>
<td>11</td>
<td>32</td>
<td>48</td>
<td>-18</td>
<td>3.8559</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>R</td>
<td>22</td>
<td>66</td>
<td>-6</td>
<td>10</td>
<td>4.7396</td>
</tr>
</tbody>
</table>

Note: Images were thresholded so that only regions significant with \( t \) values > 2.5 were shown here. The presence of significant focal changes was evaluated by thresholding the image (\( P < 0.05 \)).

BA, Brodmann area; L, left; R, right.

Table 3. Brain regions showing significant differences between stuttering condition and non-stuttering condition in the stutterers

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>BA</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentral gyrus</td>
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<td>4</td>
<td>-48</td>
<td>0</td>
<td>6</td>
<td>2.5346</td>
</tr>
<tr>
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<td>6</td>
<td>6</td>
<td>26</td>
<td>38</td>
<td>3.3064</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>9</td>
<td>-42</td>
<td>58</td>
<td>6</td>
<td>2.9291</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>21</td>
<td>40</td>
<td>10</td>
<td>-40</td>
<td>3.1277</td>
</tr>
<tr>
<td></td>
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<td>9</td>
<td>-4</td>
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<td>34</td>
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<td></td>
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<td>-42</td>
<td>58</td>
<td>6</td>
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<tr>
<td></td>
<td>L</td>
<td>11</td>
<td>-40</td>
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<td>-14</td>
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<tr>
<td>Superior parietal lobule</td>
<td>L</td>
<td>7</td>
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<td>-68</td>
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<tr>
<td>Parahippocampal gyrus</td>
<td>L</td>
<td>27</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
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<td>-20</td>
<td>-28</td>
<td>3.1509</td>
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<td>Anterior cingulate</td>
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<td>24</td>
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<td>Anterior cingulate</td>
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<td>-10</td>
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<tr>
<td>Anterior cingulate</td>
<td>R</td>
<td>33</td>
<td>6</td>
<td>20</td>
<td>22</td>
<td>3.2263</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
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<td>24</td>
<td>12</td>
<td>14</td>
<td>30</td>
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<tr>
<td>Cingulate gyrus</td>
<td>L</td>
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<td>-18</td>
<td>-42</td>
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<tr>
<td>Caudate tail</td>
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<td>36</td>
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<td>16</td>
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<td>2.9641</td>
<td></td>
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Note: Images were thresholded so that only regions significant with \( t \) values > 2.5 are shown here. The presence of significant focal changes was evaluated by thresholding the image (\( P < 0.05 \)).

BA, Brodmann area; L, left; R, right.
PET in Chinese Stutterers

One limitation of this study is small case number. Although we initially recruited 10 stutterers, 6 of them showed relative fluency during PET scanning, only 4 patients’ data were used in statistical analysis. Another limitation is lack of long-term follow-up; therefore, we do not know if the brain activation changes after treatment or spontaneously after a long period of time.

CONCLUSION

In conclusion, although differences exist between Mandarin Chinese (a logographic system) and alphabetic languages such as English (a phonologic system), this study did not show much difference in brain activation during stuttering condition between English-speaking stutterers and Mandarin Chinese-speaking stutterers. Previous study showed that more right cortical regions were involved in reading Mandarin Chinese relative to reading English, because the square shape of the logograph in Mandarin Chinese requires a particular analysis of spatial information of various strokes. [9] In our study, over-activation of right brain structure is more due to the influence of stuttering, rather than due to reading Mandarin Chinese, because of cancelling out during data reduction.

ACKNOWLEDGEMENT

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REFERENCES


中文口吃患者腦活化之正子造影研究

曾鳳菊 1  徐榮隆 2,7  陳遠光 3,4  謝霖芬 1,4  王宏哲 5  柴發順 6  趙雅苓 1

新光吳火獅紀念醫院 復健科 1  神經內科 2  核子醫學科 3  正子造影中心 6
天主教輔仁大學醫學系 4  國立陽明大學腦科學研究所 5  台北醫學大學醫學資訊研究所 7

雖然英語口吃者之神經影像研究過去曾有學者發表，但針對中文口吃者以正子造影研究腦部活化之報告，卻鮮少有人發表。本研究的目的是要以正子造影探討中文口吃者之腦部活化型態。

每位受試者均接受 18-氟-去氧葡萄糖正子造影之測試，其中口吃者為 4 位說中文男性，平均 30.75 歲，每位均接受兩次掃描，一為單獨朗讀時(solo reading，即口吃狀態)，另一為一起朗讀時(choral reading，即非口吃狀態)；而正常人(4 位說中文男性，平均 26.75 歲)只在單獨朗讀時測試。

測試的結果發現口吃者在單獨朗讀及一起朗讀時，正子造影顯示之大腦活化有顯著的差異(P 值 < 0.05)。口吃者在單獨朗讀時大腦的活化偏向右邊，而活化區域則包括上額回(BA11)，中額回(BA8，9)，下額回(BA45-47)，中央後回(BA1-3，43)及上額回(BA22)等。

此外，口吃者單獨朗讀與一起朗讀時比較，其腦部活化亦顯著增加，包括雙側內側額回(BA6，9-11，21)，雙側額回(BA24，31-33)，雙側海馬旁回(BA27，36)，左側中央前回(BA4)，左側尾核體及右側尾核尾。

結論：中文口吃者之正子造影研究發現右腦活化有增加(或左腦活化減少)之現象，活化的範圍包括運動皮質區及初級聽覺皮質區。此現象與英文口吃者相似，顯示口吃者大腦之口語流暢迴路有缺陷，因而造成其語言自我監控之障礙。(台灣復健醫誌 2012；40(1)：9 - 17)

關鍵詞：口吃(stuttering)，正子造影(PET)，中文(Chinese)

通訊作者：謝霖芬醫師，新光吳火獅紀念醫院復健科，台北市 111 士林區文昌路 95 號
電話：(02) 28332211 轉 2538    E-mail：M001026@ms.skh.org.tw