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A positron emission tomography [18F]deoxyglucose study of developmental stuttering

Joseph C. Wu,[CA] Gerald Maguire, Glyndon Riley,[1] James Fallon, Lori LaCasse, Sam Chin, Eric Klein, Cheuk Tang, Stephanie Cadwell and Stephen Lottenberg

University of California, Irvine Brain Imaging Center, Department of Psychiatry, Room 163 Irvine Hall, Irvine, CA 92717; [1]California State University, Fullerton Communicative Disorders Program Fullerton, CA, USA

[CA] Corresponding Author

POSITRON emission tomography using [18F]deoxyglucose (FDG) as a marker of regional brain metabolism was used to investigate the neural substrate of stuttering. Four patients with severe developmental stuttering were studied while reading aloud to another person (stuttering condition) and while reading aloud in unison with someone else (non-stuttering condition). The patients were also compared with four normal controls reading aloud by themselves. In the stuttering condition, significant decreases in regional glucose metabolism in Broca's area, Wernicke's area and frontal pole were seen compared with themselves while not stuttering. These differences were also seen in stuttering condition compared with normal controls. Significantly lower left caudate metabolism was seen in patients during both stuttering and non-stuttering conditions compared with normal controls. A circuit for stuttering is proposed based on these findings.

Key words: Positron emission tomography (PET); Broca's area; Wernicke's area; Caudate; Stuttering; Cingulate; Frontal cortex

Introduction

Stuttering is a speech disorder characterized by frequent repetition or prolongations of sounds or syllables. Other features include silent blockings, circumlocutions to avoid feared words, and excessive physical tension. This disorder, by definition, is disabling, affecting one's academic or occupational achievement or social communication.[1] The extent of the disturbance varies and is often more severe when there is special pressure to communicate. The prevalence of stuttering is approximately 1% with the vast majority of individuals (98%) affected before 10 years of age and a male to female ratio of 3:1.[1] Previous research related to stuttering neurophysiology has failed to identify a specific abnormal circuit of brain activity, although specific brain structures seem to be involved. Ludlow investigated 10 subjects who sustained penetrating brain lesions and developed acquired stuttering[2] (a much less common form of stuttering than the childhood onset, developmental form). All 10 subjects were found to have lesions in either the pyramidal or extrapyramidal motor systems, with 80% showing lesions in the caudate and lentiform nucleus, and 50% showing injury to the cerebellum. Andy and Bhatnager[3] reported the reduction of acquired stuttering symptoms in four patients using mesothalamic stimulation. Wood *et al*,[4] utilizing SPECT (single photon emission computed tomography), studied two young adult stutterers, one with acquired stuttering (secondary to a head injury at age 13), and one with developmental stuttering (with reported onset before age 4). Both subjects exhibited increased cortical blood flow in the anterior regions of the right hemisphere compared with homologous areas of the left hemisphere during stuttering. Under a fluent condition (utilizing haloperidol), the subjects showed greater blood flow in the left than the right hemisphere anterior regions. Pool,[5] in a more recent SPECT study, found absolute blood flow to be globally reduced by approximately 20% in individuals who stutter compared with controls. The greatest asymmetry between stutterers and controls was found in the anterior cingulate and in the superior and middle temporal gyri. The authors consider their findings consistent with prior reports of speech motor initiation localized in the left cingulate or supplementary motor area.

The purpose of this study was to investigate the cerebral neurophysiology of stuttering in depth utilizing PET (positron emission tomography), a technique with greater resolution than that of the previous SPECT research. One goal of the study was to identify state-dependent changes in the brains of individuals who stutter by scanning the same individuals twice, once during a stuttering condition (reading alone) and once during a fluent condition (choral reading.) Individuals who stutter may be induced to be fluent while performing various tasks including choral reading.[6] A second goal of the study was to investigate the possibility of non-reversible trait differences in the cerebral neurophysiology of individuals who stutter compared with normal controls.

Subjects and Methods

Subjects: Four adult stutterers and four normal controls were studied utilizing [18F]deoxyglucose positron emission tomography (FDG PET). All subjects were

right-hand, right-eye and right-foot dominant. All subjects had a screening physical examination and medical history taken, and all provided written, informed consent regarding the study in accordance with the Human Subjects Research Committee of UC Irvine. The stuttering subjects all had developmental stuttering with the onset of symptoms before 9 years of age. The speech of the subjects who stutter was measured objectively at least three times over a 6 week period[7] to obtain an accurate assessment of stuttering severity. The stuttering subjects had an SSI-3 score mean of 33.5 (range 29–40), with a mean of 16% stuttered syllables (range 12–21) while solo reading (reading aloud by themselves) and < 0.5% stuttered syllables during choral reading (reading aloud the same words at the same time with another individual). Subjects were excluded from participating if they had a history of a major psychiatric disorder (major depression, schizophrenia, bipolar disorder, or obsessive-compulsive disorder), or history of a life-threatening neoplasm within the last 5 years. The stuttering subjects were composed of three men and one woman with mean age of 41.5 years (range 20–54). The controls also comprised three men and one woman with a mean age of 29.5 years (range 22–41.)

Procedures: Two PET scans were performed using a method previously described[7] with a reading task. FDG was chosen as a marker because it would allow for an integrated view of the regional metabolic processes that underlie the speech process during the stuttering or the fluent state. Ten minutes before the FDG injection, the subjects received instruction in solo or choral reading; 3 min before injection, the reading task was started in order that the initial novelty of the task should not be FDG labeled. Nine slices at 10 mm intervals were obtained beginning at about 85% of head height (vertex to CM line.)

The subjects who stuttered had two separate PET scans, one during a stuttering condition (reading aloud by themselves to another person) and one during a fluent condition (choral reading, i.e. reading aloud in unison with another person) for 30 min in an acoustically attenuated testing room. The same readings were used for each condition. (The readings were non-emotionally laden articles from news magazines.) The stuttering and fluent scans were counterbalanced. The duration of the scan was 90 min. The total duration between beginning of reading and end of brain imaging was 2 h. At least 24 h separated the two scans. The normal controls had one scan following solo reading. The controls read aloud the same readings in the same room as the stuttering subjects.

Data analysis: PET images were reconstructed using standard methods.[9–11] PET images were anatomically normalized using the coordinate system of the Talairach atlas.[11] One-tailed *t*-tests were performed comparing pixels from normal controls with corresponding pixels from subjects who stutter. One-tailed *t*-tests were chosen since a review of the literature had generated *a priori* hypotheses regarding the structural lesions postulated for stuttering (e.g. caudate,[2] cerebellum,[2] thalamus,[3] cingulate,[5] superior and middle temporal gyri[5]; see Introduction). Paired *t*-tests were performed for stuttering subjects comparing their non-stuttering condition with their stuttering condition. Localization of areas of increased or decreased metabolism was performed using an overlay of Brodmann defined regions from MRIs. Images were thresholded so that only regions significant with *t*-values > 3.2 were displayed.

Results

Several brain structures showed decreased glucose uptake during the stuttering state in the individuals who stuttered compared with themselves while fluent, and in the stutterers compared with normal controls ($p < 0.05$). These areas of overlap fell into four basic

Table 1. PET study of stuttering

Brain region	Brodmann area no.	Stereotaxic coordinates				% decrease	Function
		x left	right	y ant/pos	z height		
A. Trait-related, state dependent brain regional changes							
1. superior frontal	BA9		right (–32)	45	35	56	association
2. Wernicke's area	BA39,40	left (37)		–61	35	26	auditory
3. Broca's area	BA45	left (49)		44	8	56	motor speech
4. posterior cingulate	BA23	left (14)	right (–6)	–58	8	40	limbic
5. prefrontal cortex	BA10	left (6)		53–63	8	40	association
6. deep frontal orbital	BA11	left (32 to 24)		36	–4	21	limbic
7. medial cerebellum			right (4)	–42	–4	26	timer
B. Non-trait related, state dependent, brain regional metabolic change in fluency							
1. substantia nigra		left (4)	right (–4)	19	–4	31	dopamine
C. Trait-related brain regional metabolic abnormality							
1. caudate		left (6)		18	8	47	gate valve

(all Brodmann area designations are approximate).
Stereotaxic coordinates refer to medial–lateral position (x) relative to midline (positive = left), anterior–posterior position (y) relative to the anterior commissure (positive = anterior), and height (superior–inferior). The presence of significant focal changes was evaluated by thresholding the image ($p < 0.05$). *A priori* hypothesis was established for regions based upon a review of the neuropsychological literature for stuttering. Designation of Brodmann areas is approximate.

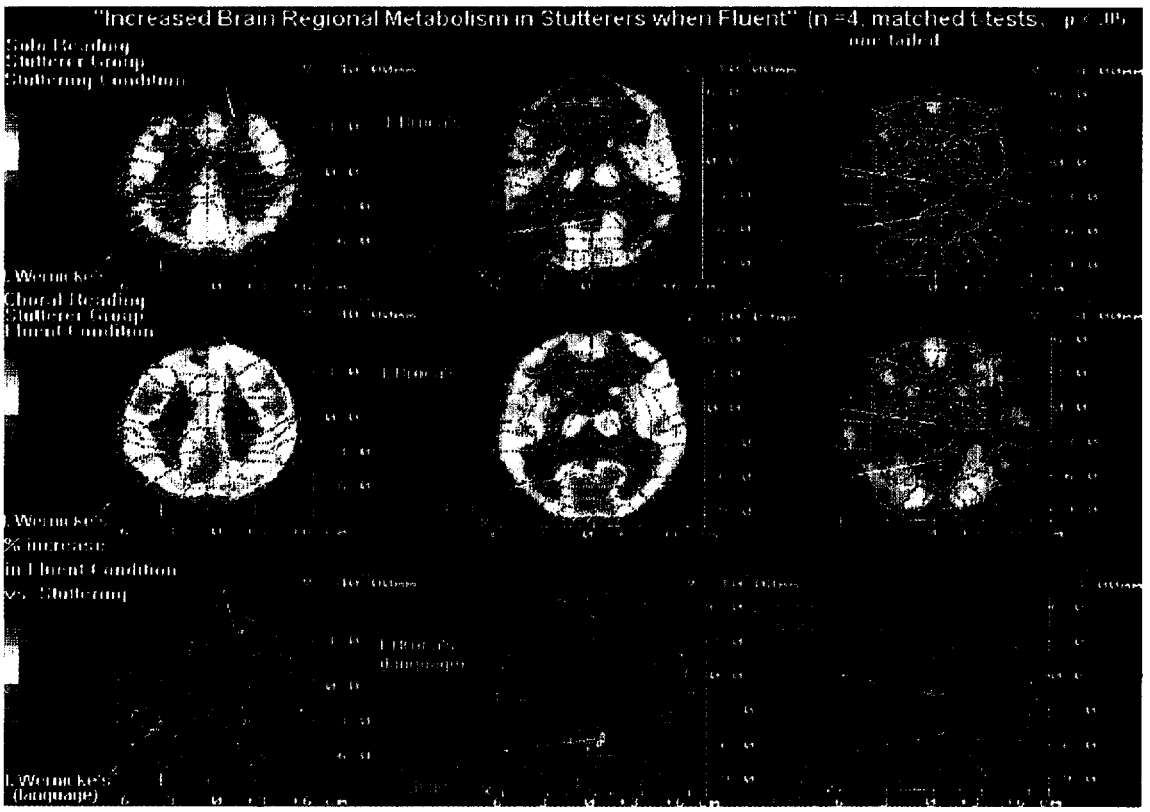


FIG. 1. Averaged PET images were created for the stutterers during their stuttering condition and during their non-stuttering condition. Averaged matched *t*-test subtraction images were created comparing the stuttering subject's individual PET slice for both conditions. The subtraction images were thresholded to display only regions significant at $p < 0.05$. The significant displayed pixels were then color coded to signify relative magnitude of change in percentage.

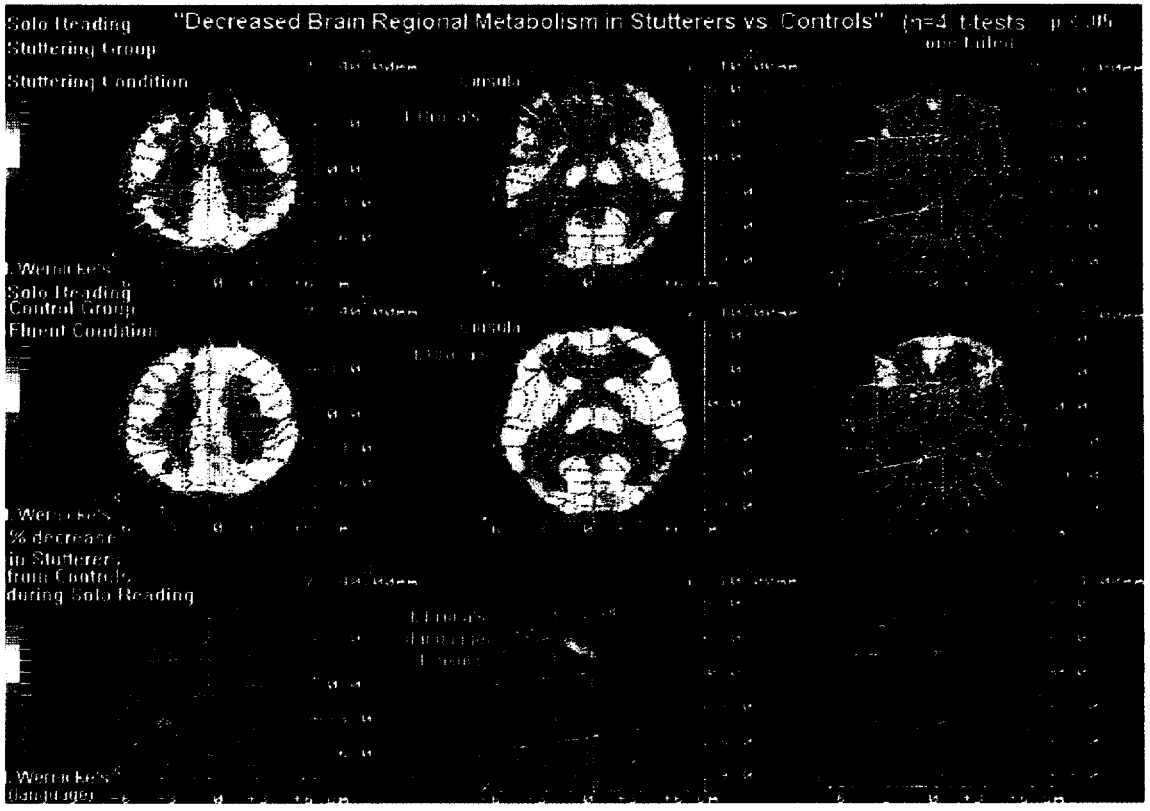
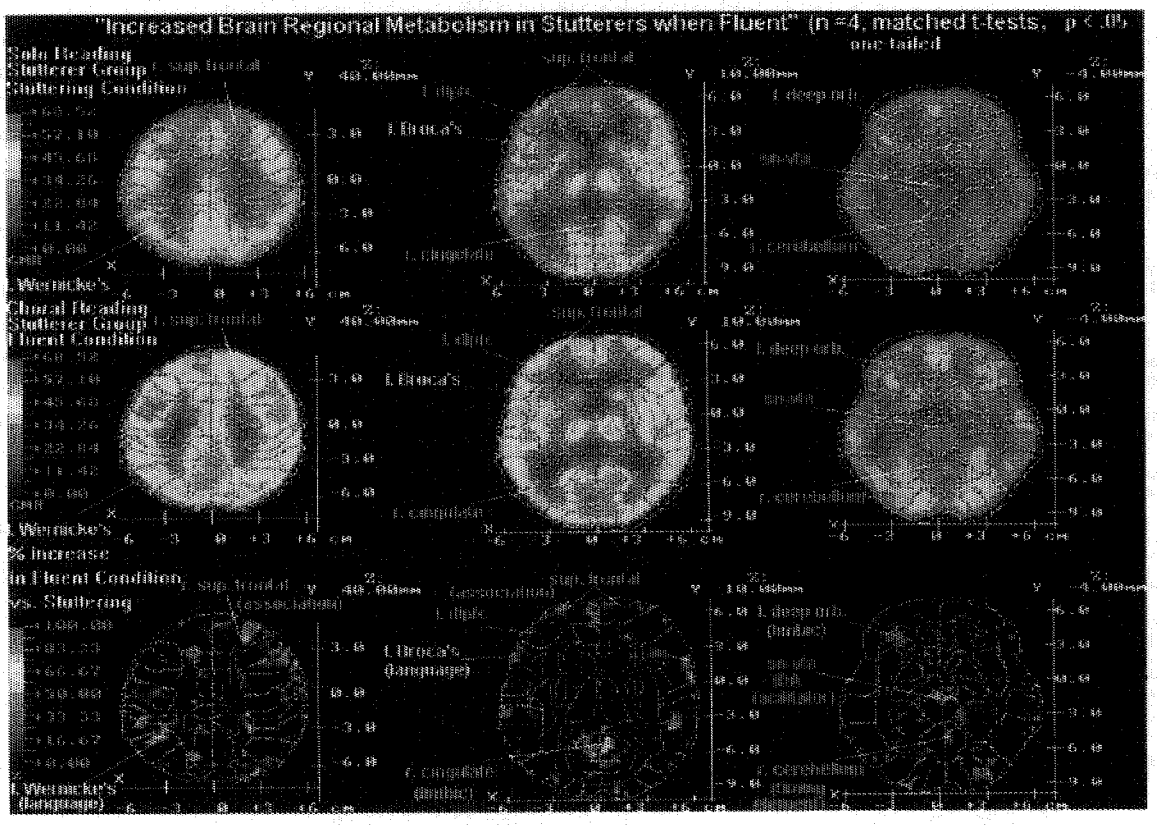


FIG. 2. A similar process was used to generate average PET images for the normal controls. A subtraction image was generated comparing the normal controls with the stutterers during their reading aloud by themselves to another person condition. Regions which overlapped between the first subtractions and the second subtractions are outlined in Table 1.



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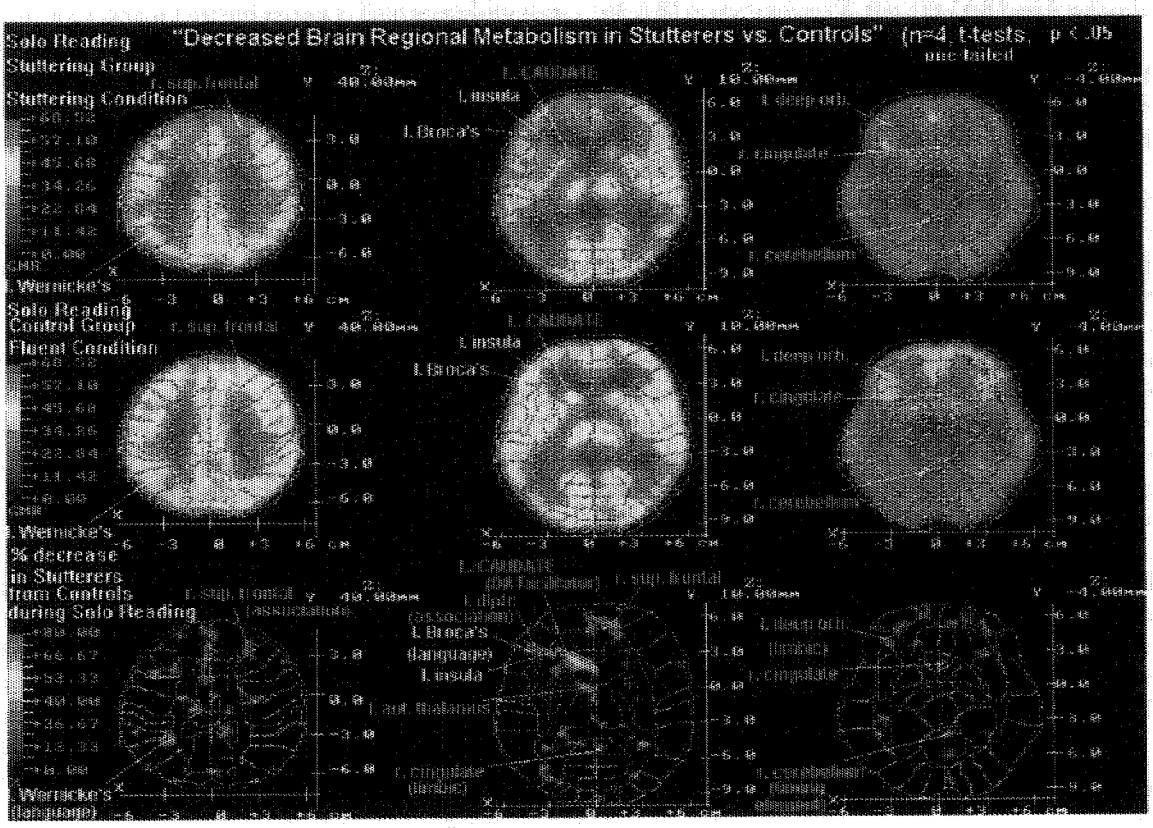

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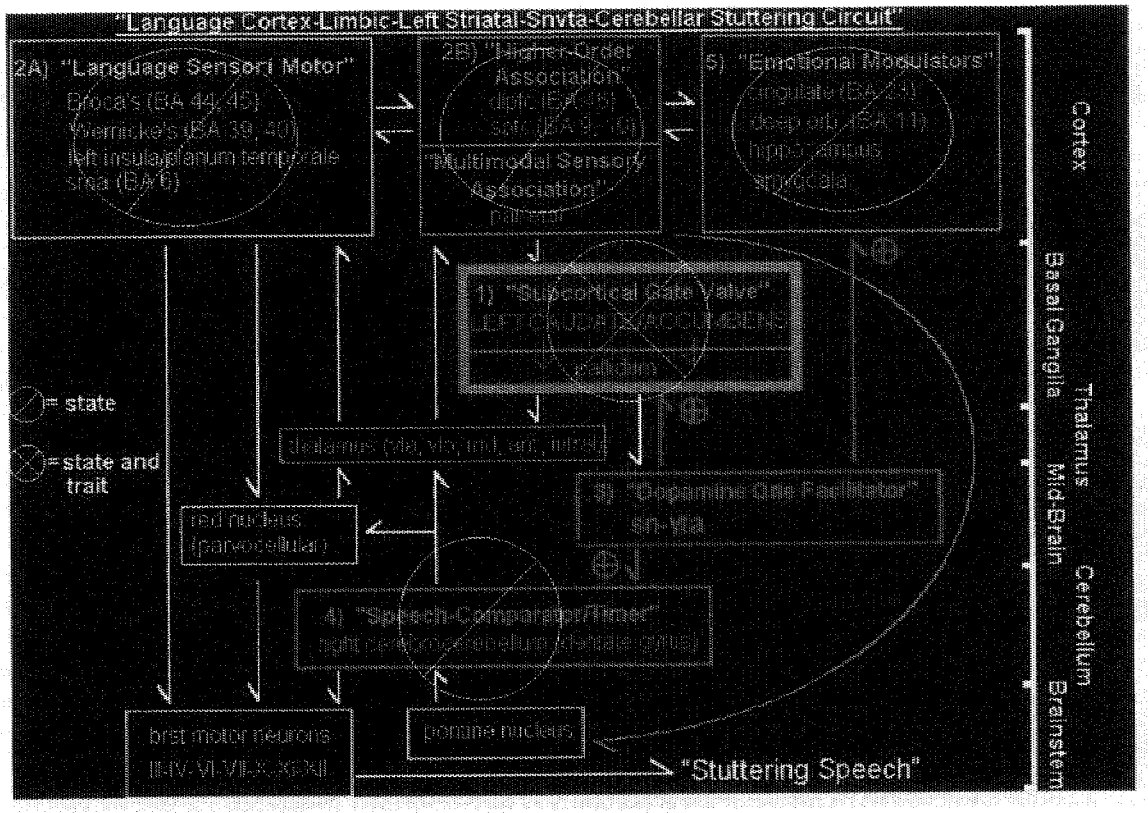


FIG. 3. A color coded circuit for stuttering is proposed based on the findings in the above subtractions.

categories: (A) left language areas: left Broca's area (Brodmann Area [BA] 45), left Wernicke's area (BA 39, 40); (B) higher order association areas: left superior frontal lobe (BA 10), right superior frontal lobe (BA 9); (C) right cerebellum; (D) limbic areas: left deep frontal orbital (BA 11) and bilateral posterior cingulate cortex (BA 23) (see Table 1A and Figs 1 and 2). Overall, no regions showed greater activity during the stuttering state than during either the choral reading state or the reading state of the normal controls.

Overall, the choral reading scans of the individuals who stuttered resembled those of the normal controls with two notable differences. In addition to the brain areas of overlap described above, the brains of individuals who stuttered showed that the left caudate has the largest difference between stutterers and controls with 2 regions of decreased glucose uptake during the solo reading task compared with the brains of normal controls performing the same solo reading task (Table 1B and Fig. 1). The caudate failed to show any normalizing increase during the non-stuttering condition. During the induced fluent state, the substantia nigra showed supranormal levels of activation in stutterers [Table 1C and Fig. 1].

Discussion

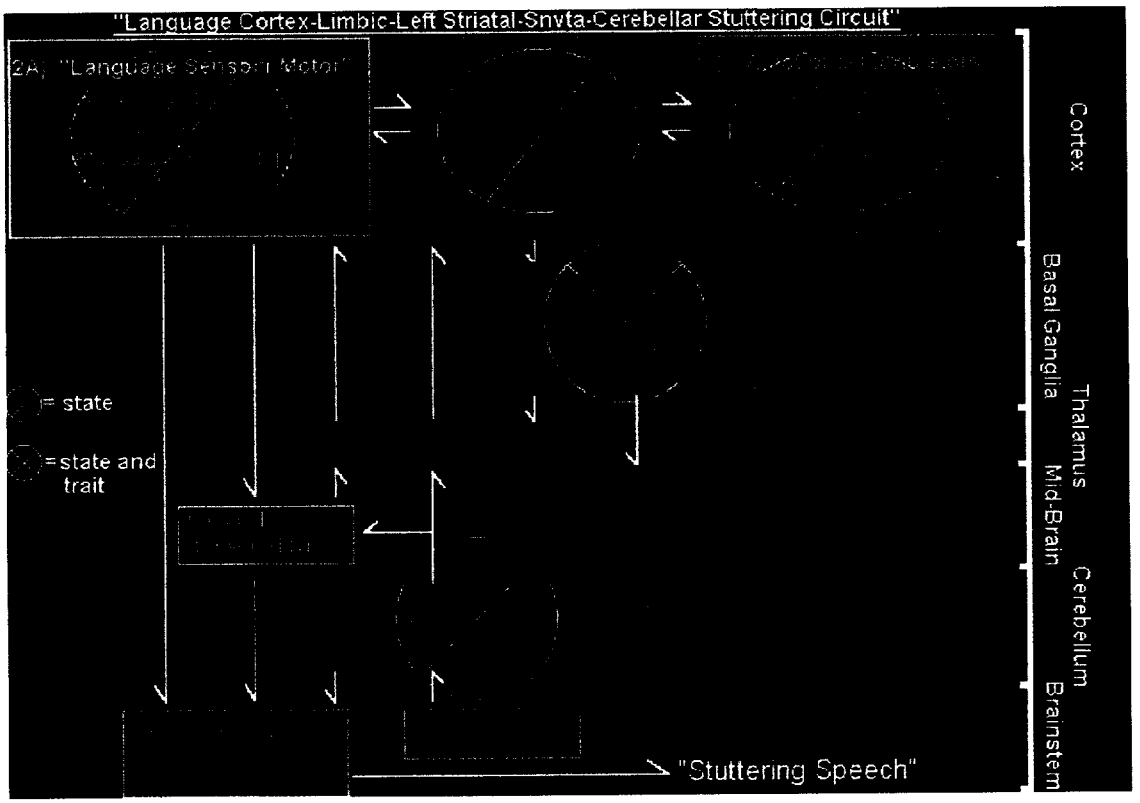
The findings described above suggest that stuttering may arise from a functional neuroanatomical circuit defect of five components (Fig. 3).

The first component is permanent left caudate hypometabolism which is a possible trait marker for stuttering. During the stuttering state, the left caudate appears to be approximately 50% less active in stutterers than in normal controls. Even during fluency induced by choral reading the individuals who stuttered still had significantly lower left caudate metabolism compared with controls. These observations imply that individuals who stutter have significantly lower caudate metabolism whether they are fluent or dysfluent compared with controls.

The second is reversible metabolic hypoactivity in the left language circuit (Broca's area and Wernicke's area),[13,14] and higher order association areas (superior frontal cortex). These regions may represent a state dependent circuit that can be increased to normal functioning during induced fluent states in individuals who stutter.[15] The third component is an increase to supranormal levels of substantia nigra/ventral tegmental area neuronal firing in the midbrain during the induced fluent state.

The fourth component of the circuit is the right cerebellum as timing element/comparator corrector. Activity in the cerebellum was lower in the stutterers while they were stuttering than when they were fluent and compared with controls. However, the activity of the right cerebellum normalized to that of the normal controls during the choral reading task.

The fifth component of the stuttering circuit is the limbic system (i.e. posterior cingulate), which acts as



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The fifth component of the stuttering circuit is the limbic system (i.e. posterior cingulate), which acts as

the emotional modulator.[16] Anxiety, which is centered in the limbic system, makes stuttering worse. The activity of the limbic system is increased in the individuals who stutter when they are fluent.

Comparisons between groups (e.g. stutterers *vs* normals) will have less similar anatomical comparability than comparisons within groups (e.g. stutterers fluent when choral *vs* stutterers dysfluent during solo reading). The within-group comparison has the advantage of using subjects as their own anatomical control. Nevertheless, comparisons using normalized data between groups have been utilized by numerous investigators (e.g. Roy John *et al*[17]) to study PET differences between different populations.

Conclusion

Stuttering is associated with specific cerebral regions of decreased activity in Broca's area, Wernicke's area, frontal pole, cingulate cortex and cerebellum. Many of these regions are activated when individuals who stutter are induced to be fluent. A persistent defect is found in the left caudate whether stutterers are stuttering or fluent. Substantia nigra regions show supranormal activity during temporary fluency. Limitations of this study however, include the small number of subjects studied, and the 12-year age difference between normal controls and subjects. Future PET research will include the study of more subjects and better age-matched controls.

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